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Acute Ischemic Heart Disease

Is the measurement of left ventricular ejection fraction the proper end point for cell therapy trials? An analysis of the effect of bone marrow mononuclear stem cell administration on left ventricular ejection fraction after ST-segment elevation myocardial infarction when evaluated by cardiac magnetic resonance imaging

Jay H. Traverse, MD,[a,b,c] Timothy D. Henry, MD,[a,b,c] and Lemuel A. Moye', MD, PhD[c,d]
Minneapolis, MN; and Houston, TX

Background The measurement of left ventricular (LV) ejection fraction (LVEF) is a strong predictor of cardiovascular adverse events and mortality in patients with LV dysfunction and has become the most common primary end point in cardiovascular cell therapy trials after ST-segment elevation myocardial infarction (STEMI). Multiple small trials have been performed using bone marrow mononuclear stem cells (BMCs) in this setting with several meta-analyses demonstrating that BMC administration results in a small improvement in LVEF and may attenuate adverse LV remodeling. However, individual trial results have not been uniform, and the measurement of LVEF in these trials has relied on a variety of imaging techniques including LV angiograpnhy, single-photon emission computed tomography, echocardiography, or cardiac magnetic resonance imaging (cMRI).

Methods Because cMRI provides the most accurate measurement of LVEF, LV volumes, and infarct size in patients after STEMI, we reviewed all randomized cardiovascular stem cell trials (N = 10) that administered intracoronary BMCs versus placebo/control to 686 patients after primary percutaneous coronary intervention treatment of STEMI that used cMRI as their principal imaging measurement of LVEF at baseline and 3 to 6 months later.

Results Administration of BMCs was associated with a nonsignificant 0.9% ± 0.8% absolute increase in LVEF compared with placebo or control (95% CI –0.7 to 2.4) with a small but nonsignificant decrease LV end-diastolic and LV end-systolic volumes (LV end-diastolic volume –1.1 ± 1.5 mL/m^2, LV end-systolic volume –1.6 ± 1.4 mL/m^2). Although infarct size uniformly decreased over time, the reduction was not improved by BMC administration (–0.3 ± 1.7 g).

Conclusions The benefit of BMC administration after STEMI on LVEF, LV volumes, and infarct size is small when assessed by cMRI. (Am Heart J 2011;162:671-7.)

>1,000 patients have been enrolled in randomized cardiovascular cell therapy trials throughout the world using intracoronary bone marrow mononuclear stem cells (BMCs) after ST-segment elevation myocardial infarction (STEMI). The administration of BMCs in patients after STEMI appeared logical because of the large amount of accumulated preclinical data demonstrating significant recovery of left-ventricular (LV) function after coronary ligation and infarction in animals receiving cell therapy.[1]

The initial observational studies of Strauer et al[2] who administered intracoronary BMCs in patients after STEMI demonstrated the safety and utility of this approach. Based on these encouraging findings, multiple randomized, controlled studies, predominantly from Europe, have been performed. Recent meta-analyses of cell therapy trials[3-5] have demonstrated that cell therapy administration post STEMI is associated with a small improvement in LV ejection fraction (LVEF) and

From the [a]The Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis, MN, [b]The University of Minnesota Medical School, Minneapolis, MN, [c]The Cardiovascular Cell therapy Research Network (CCTRN) Houston, TX, and [d]The University of Texas School of Public Health, Houston, TX.
Submitted February 8, 2011; accepted June 21, 2011.
Reprint requests: Jay H. Traverse, MD, Minneapolis Heart Institute, 920 East 28th St, Suite 300, Minneapolis, MN 55407.
E-mail: trave004@umn.edu
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Table I. Study design

Study	Placebo or control group	Primary end point	No. of cells delivered $\times 10^6$	Cell separation media	Cell storage media
Hirsch et al,[9] HEBE trial	Control	% Improvemnt of dysfunctional segments	296 ± 164	Lymphoprep	4% HSA
Wohrle et al[10]	Placebo	LVEF	381 ± 130	Ficoll	2% HSA
Tendera et al,[11] REGENT	Control	LVEF	178 (median)	Ficoll	PBS
Wollert et al,[13] BOOST trial	Control	LVEF	2460 ± 940	4% gelatine-polysuccinate	5% AS
Janssens et al[8]	Placebo	LVEF	304 ± 128	Ficoll	5% AS
Lunde et al,[7] ASTAMI Trial	Control	LVEF	68 (54-130) median	Lymphoprep	Plasma + overnight storage, 4°C
Traverse et al[15]	Placebo	LVEF	100	Ficoll	5% HSA
Dill et al,[16] REPAIR-AMI	Placebo	LVEF*	236 ± 174	Ficoll	X-Vivo 10 + 20% AS + overnight storage, RT
Roncalli et al,[12] BONAMI	Control	Viability-SPECT	98 ± 8.7	Ficoll	4% HSA
Huang et al[14]	Placebo	LVEF	180 ± 42	Ficoll	AS

HSA, Human serum albumin; *AS*, autologous serum; *PBS*, phosphate-buffered saline; *RT*, room temperature; *SPECT*, single-photon emission computed tomography; WMSI, wall motion score index.
*Measured by LV angiography; all other studies measured LVEF by cMRI.

attenuation of adverse LV remodeling compared with placebo or control. However, the measurement of LVEF was not uniform because a variety of imaging techniques were used including left ventriculography, single-photon emission computed tomography, echocardiography, and cardiac magnetic resonance imaging (cMRI).

Cardiac magnetic resonance imaging is widely accepted as the criterion standard of cardiac imaging in the setting of STEMI and LV dysfunction because of its high resolution and freedom from geometric assumptions.[6] In addition to accurate measurements of LVEF and chamber dimensions, it simultaneously allows measurement of infarct size, microvascular obstruction, and myocardial edema to determine area at risk. This imaging technique is now widely used in cell therapy trials. Given its increased accuracy, a close examination of the effects of BMC administration on LVEF in trials that have used cMRI as their primary imaging modality may provide unique insights into the benefits of cell therapy because most of these trials have not been included in previous meta-analyses.

Methods

We reviewed all trials that administered intracoronary BMCs after primary percutaneous coronary intervention (PCI) treatment of STEMI that used cMRI as one of its principle measurements of LVEF and volumes. We identified 10 trials[7-16] that fulfilled the above criteria comprising 378 patients randomized to BMCs and 308 patients randomized to placebo or control that had paired cMRI data available for review (Table I). Follow-up cMRI data were used in our analysis at the stipulated end point of 3 to 6 months despite several trials having longer term follow-up data available (1-3 years).[17-19] For the REPAIR-AMI trial, we used only those patients reported in the magnetic resonance imaging (MRI) subgroup analysis.[16]

Measurements of LV end-systolic (LVESV) or end-diastolic (LVEDV) volumes were expressed as milliliters per square meter. In 4 trials,[7,11,14,16] data for LVESV and LVEDV were reported as milliliters. To facilitate comparisons between studies, the LV volumes in those 4 trials were normalized by dividing by the body surface area for a typical 80-kg male patient. Infarct size was reported in 8 of the 10 studies. Of the 8 studies, 3 studies[10,12,14] reported infarct size in %LV instead of grams or milliliters and were not included in the calculation of the overall BMC treatment effect.

Statistical analysis

For measurements of LV function, we examined the LVEF, LVEDV, LVESV, and infarct size and computed the mean change in the BMC group minus the mean change in the control group. Using the weighted general linear model, we computed the mean control group adjusted change associated with BMCs for each of these 4 variables and the SE of this change. All test statistics are mean change divided by the SE. All *P* values are 2 sided and based on the normal distribution.

The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper and its final content. No extramural funding was used to support this work.

Results

The mean dose of BMCs (total nucleated cells) delivered in the trials ranged from 68 × 10^6[7] to 2,460 × 10^6.[13] The intracoronary delivery of BMCs varied from the day of PCI[14] to mean of 9 days after PCI.[12] Baseline cMRI was performed as early as 4 days before BMC infusion[16] and up to 18.8 ± 4.3 days after PCI.[7] Most trials performed their follow-up cMRI at 6 months, whereas 2

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Transplant day post PCI	Day of MRI post PCI	Follow-up (m)	Treatment effect of BMCs to improve LVEF vs control	Secondary LV functional end points
6 (3-8)	2-7	4	*P* = .94	Segmental wall thickening of dysfunctional segments
6.1 (5.5-7.3)	6	6	*P* = .10 (favored placebo)	
7 (3-12) median	8-11	6	*P* = .17	
4.8 ± 1.3	3.5 ± 1.5	6	*P* = .0026	Regional LVEF; Systolic wall thickening
Within 24 h	4	4	*P* = .36	Systolic wall thickening Strain-rate
6 (5-6) median	18.8 + 4.3	6	*P* = .054 (favored control)	
5.2 ± 2.3	3.3 ± 2.3	6	*P* = .425	
4.3 ± 1.3	−4 to 6 p Cell transplant	4	*P* = .26 (12 m), cMRI subgroup *P* = .01 (4 m), entire cohort	Systolic wall thickening in infarct region
9.3 + 1.7	7.1 + 2.3	3	*P* = .90	WMSI
0	7	6	*P* = .047	

trials performed the follow-up cMRI at 4 months[9,16] and 1 at 3 months.[12] All studies with the exception of two[14,15] delivered intracoronary BMCs by the "stop-flow" technique through a percutaneous transluminal coronary angioplasty catheter.

The mean LVEF in the BMC group between baseline and 3 to 6 months later increased from 45.5% ± 2.7% to 49.2% ± 2.7%, whereas the LVEF in the placebo or control group increased from 45.4% ± 2.6% to 48.2% ± 3.0%. This resulted in a nonsignificant placebo-adjusted absolute change in LVEF of 0.9% ± 0.8% (95% CI −0.7 to 2.4) that could be attributed to cell therapy (Table II). The mean LVEDV increased slightly in the BMC group from 78.7 ± 5.1 mL/m^2 to 82.5 ± 5.5 mL/m^2 at follow-up and was not different from the change in the control group, resulting in a nonsignificant treatment effect of −1.1 ± 1.5 mL/m^2 (95% CI −4.1 to 1.1) (Table II). No significant treatment effect was observed on LVESV, which was unchanged in the BMC group and increased slightly in the control group (41.2 ± 4.0 mL/m^2 to 42.8 ± 4.4 mL/m^2). Infarct size uniformly decreased over time in both the BMC and control groups, but no treatment effect was observed (−0.3 ± 1.7 g, 95% CI −3.5 to 3.0) (Table II).

Discussion

In this review, we observed that the administration of intracoronary BMCs to randomized patients up to a mean of 9 days after primary PCI for STEMI had a negligible effect on LVEF, myocardial volumes, and infarct size reduction when measured by cMRI 3 to 6 months later. Although at least 3 previous meta-analyses have been performed that have examined the effects of cardiovascular cell therapy, our analysis is unique in that it is confined to only those trials that administered intracoronary BMCs after STEMI and used cMRI for measurements of their primary end points. Our study contains at least 5 new trials not included in any previous meta-analyses.

The first meta-analysis of cardiovascular cell therapy was published by Abdel-Latif et al[3] in 2007 of 999 patients. In addition to BMC administration, the report included trials that administered mesenchymal and progenitor cells and included patients with chronic ischemia. Lipinski et al[4] first analyzed mononuclear cell therapy in the setting of STEMI in 698 patients. In addition to nonrandomized trials, they included several trials that administered granulocyte colony stimulating factor for peripheral harvest of mononuclear cells or administered selected CD133$^+$ cells. They observed a significant treatment effect of BMCs on cardiac function where LVEF increased by 3% and LVESV decreased by 7.4 mL. Only 4 of the 10 trials in our analysis were included in their report. Martin-Rendon et al[5] performed the first meta-analysis of randomized, controlled trials using BMCs after STEMI in 811 patients. They observed a similar treatment effect of 3% on LVEF and a 4.7-mL reduction in LVESV and a small but nonsignificant reduction in LVEDV (2.5 mL). Subgroup analysis suggested that a beneficial effect of BMC therapy was only observed when at least 100 million cells were delivered. Their analysis included 5 of the 10 trials included in our report.

Although our report is not a formal meta-analysis, the calculation of treatment effects is similar to these previous reports. We observed a nonsignificant 0.9% improvement in LVEF and no benefit on LV volumes and infarct size reduction after administration of BMCs 3 to 6 months

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Table II. Changes in LVEF, LVEDV, LVESV and infarct size

	LVEF (%)						LVEDV (mL/m^2)					
	BMCs		Control				BMCs		Control			
Study	**n**	**δ**	**n**	**δ**	**Mean**	**SE**	**n**	**δ**	**n**	**δ**	**Mean**	**SE**
Hirsch et al,[9] HEBE trial	67	3.8	66	4.0	−0.20	1.73	67	5.4	60	8.2	−2.80	4.82
Wohrle et al[10]	29	1.8	13	5.7	−3.90	3.70	29	9.6	13	10.5	−0.90	8.25
Tendera et al,[11] REGENT trial*,‡	46	3.0	20	0.0	3.0	2.97	46	5	20	1.5	6.5	5.16
Wollert et al,[13] BOOST trial	30	6.7	30	0.7	6.0	3.18	30	7.5	30	3.5	4.0	7.61
Janssens et al[8]	30	3.3	30	2.2	1.10	2.52	30	2.9	30	2.8	0.10	15.9
Lunde et al,[7] ASTAMI trial*	44	1.2	43	4.3	−3.00	3.01	44	−3.5	43	−1.4	−2.1	7.29
Traverse et al[15]	30	6.2	10	9.4	−3.2	4.55	30	−4	10	17	−21.0	8.99
Dill et al,[16] REPAIR-AMI*	27	3.3	27	0.8	2.50	1.94	27	4.3	27	7.0	−2.7	6.59
Roncalli et al,[12] BONAMI trial†	48	1.9	44	2.2	−0.30	2.23	48	11.5	44	9.2	2.30	5.03
Huang et al[14]*,†	20	7.0	20	4.5	2.50	2.26	20	−6.5	20	−5.0	−1.5	4.25
Mean weighted change	BMC 45.5 ± 2.7 to 49.2 ± 2.7 CON 45.4 ± 2.6 to 48.2 ± 3.0						BMC 78.7 ± 5.1 to 82.5 ± 5.5 CON 75.9 ± 4.4 to 79.9 ± 5.4					
Treatment effect	**Mean**		**SE**		**CI**		**Mean**		**SE**		**CI**	
(95% CI)	0.9		0.8		−0.7 to 2.4		−1.1		1.5		-4.1 to 1.1	

δ, difference between baseline and final means; *Mean*, mean difference between BMC versus control/placebo; *CON*, control group.
*Data are reported in milliliters; converted to milliliters per square meter for analysis.
†Infarct size reported as % of LV (not included in overall treatment effect).
‡Data reported as median.

later. Our findings are in contrast to previous meta-analyses[3-5] in that no significant treatment effect of BMCs was observed with any of the measured parameters.

There are several potential reasons why BMC administration appeared less effective in our cMRI analysis. Most importantly, most new trials reported in our analysis observed no benefit of BMCs to improve either LVEF or remodeling.[9-12,15] These more recent trials did not differ with respect to the dose of infused cells reported in the earlier analyses. However, there was a significant difference in the time to cell delivery after PCI in which the more recent negative trials delivered cells at a later time point after PCI (6.9 vs 3.2 days, $P = .02$). In addition, there was a much wider variation in performing baseline cMRI measurements relative to PCI in some of the earlier trials compared with more recent studies. For example, the ASTAMI trial[7] performed their baseline cMRI measurements 18 days after PCI. It is possible that LVEF may have improved significantly during that time window because of resolution of myocardial stunning. Although this effect should occur equally in the treatment and placebo groups, it could effectively dilute any BMC treatment effect. Most trials reported in this analysis used Ficoll as the density gradient media for BMC isolation, whereas 2 trials used lymphoprep[7,9] and 1 study used gelatine-polysuccinate.[13] The cell storage media used was evenly distributed between human serum albumin or autologous serum. It is noteworthy that the most positive study reported to date, REPAIR-AMI,[19] was the only trial to additionally use X-Vivo-10 media in addition to 20% autologous serum with overnight storage at room temperature. Although initial reports demonstrated that the final cell recovery and activity may be inferior when using lymphoprep as opposed to Ficoll,[20] a recent analysis by Yeo et al[21] found no difference in cell recovery or distribution of cell types between the 2 agents. Importantly, the HEBE investigators,[22] who observed no improvement in LVEF with BMCs, found no difference in the functional activity of their cellular product isolated with lymphoprep compared with cells isolated using methods in REPAIR-AMI.[19] They did identify the importance of centrifugation speed as being directly correlated with cell recovery, which may explain the lower recovery of cells in the negative ASTAMI trial.[7]

Is the measurement of LVEF the proper end point for cell therapy trials?

The measurement of LVEF is a simple but powerful predictor of cardiovascular mortality in patients with LV dysfunction.[23] It is not surprising that this metric has become the most frequently used primary end point in BMC trials, expressed as the change in LVEF between baseline and a stipulated time point several months later. Although the LVEF at 4 to 6 months after STEMI may be quite stable, the LVEF at baseline may improve rapidly during the first week after STEMI because of the resolution of myocardial stunning and reperfusion injury. In the HEART trial,[24] 261 patients with anterior STEMI experienced an increase in mean LVEF from 51.7% to 55.8% by echocardiography between days 1 and 14. Ndrepepa et al[25] observed that the LVEF measured by left

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LVESV (mL/m²)						Infarct size (g or mL)					
BMCs		Control				BMCs		Control			
n	δ	n	δ	Mean	SE	n	δ	n	δ	Mean	SE
67	−0.5	60	1.2	−1.70	4.39	58	−7.7	52	−9.4	1.7	3.01
29	2.9	13	1.1	1.80	6.93						
46	−0.5	20	4.5	−5.0	4.10			Not reported			
30	−0.6	30	2.0	−2.60	7.36	30	−14.1	30	−10.5	−3.6	5.75
30	−1.2	30	0.6	−1.80	5.24	30	−10.3	30	−7.6	−2.7	4.52
44	−2.5	43	−4.5	2.00	4.62	43	−2.3	43	−5.9	3.6	5.74
30	−7.0	10	−2.0	−5.00	7.18			Not reported			
27	0.1	27	4.6	−4.50	5.40	27	−5.3	27	−2.6	−2.7	6.04
48	7.1	44	5.4	1.70	4.54						
			Not reported								
		BMC 43.0 ± 5.1 to 43.8 ± 5.9 CON 41.2 ± 4.0 to 42.8 ± 4.4						BMC 24.6 ± 7.5 to 15.2 ± 4.8 CON 26.1 ± 7.7 to 17.4 ± 4.9			
Mean		SE		CI		Mean		SE		CI	
−1.6		1.4		−4.4 to 1.1		−0.3		1.7		-3.5 to 3.0	

ventriculography increased from 51.6% just before PCI to 57.4% at 6 months in 626 patients with their first STEMI. In a BMC cell therapy trial from our institution,[15] the mean LVEF by echocardiography increased from 38.9% on day 1 to 44.6% on day 7 in 40 patients with large anterior STEMI after primary PCI. Studies using serial cMRI to measure LVEF have demonstrated a 6.3% absolute increase over the first 30 days after STEMI and up to 8.3% by 6 months after primary PCI.[26] These findings demonstrate that LVEF may significantly improve in the early period after STEMI that may result in significant variation in the true baseline LVEF used in cell therapy trials.

If the increase in LVEF because of resolution of stunning occurs in both the treatment and placebo group and if the effect of cell therapy is additive, then stunning will not bias the measurement of the change in LVEF because of BMC therapy. However, the increased variability in LVEF produced by the resolution of stunning will make it more difficult to detect a signal of the BMC effect from the background variability. As a result, this will require a much larger sample size to demonstrate a therapeutic effect. Because the choice of time interval in which stunning resolves has not been well controlled in the design of current trials, its influence has likely affected the detection of the BMC signal. Although the timing of cell therapy administration has not been previously integrated into the randomization scheme of any major cell therapy trial, it is currently being addressed in the NHLBI TIME trial[27] performed by the Cardiovascular Cell Therapy Research Network. In this trial, patients are randomized to cell therapy on days 3 versus 7 post STEMI, and cMRI measurements are performed at both days 3 and 7 to help illuminate the effect of stunning resolution from the BMC treatment effect.

The use of LVEF as a primary end point in cell therapy trials may also be problematic for other reasons. As the LVEF increases, it loses its predictive power for cardiovascular events and death. In the CHARM study,[23] the ability of an LVEF measurement to predict cardiovascular risk was lost when it exceeded 45%. It is noteworthy that most patients enrolled in cardiovascular stem cell trials exceed this 45% threshold. This trend is likely to continue, in part, because of the recent advances in regional STEMI transfer networks that reduce ischemic times in patients presenting for primary PCI. Left ventricular ejection fraction may also vary over time in response to physiologic changes of load or the presence of hypercontractile segments of remote myocardium that may inflate the global LVEF.

The use of regional myocardial function to assess efficacy of cell therapy trials

Given the potential limitations of using LVEF as a primary end point, several BMC trials also analyzed regional LV function to determine if regional changes represent a more sensitive marker of cell therapy efficacy. The BOOST trial[13] calculated both regional LVEF and regional systolic function determined as the radial displacement of the endocardial contour. At 6 months, they observed that systolic wall motion was only

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improved in the border zone and not the infarct zone, suggesting that cell therapy improved only regions without infarction. However, similar to the global LVEF, these improvements in regional function in the BMC group were not sustained at 18 months.[18] The HEBE trial[9] measured segmental wall thickening in dysfunctional segments and found no improvement in the BMC treatment group, which was concordant with their changes in global LVEF, whereas the cMRI subgroup of REPAIR-AMI observed that regional systolic wall function only improved in patients with an LVEF below the median.[16] Herbots et al[27] observed that regional LV function assessed by strain-rate imaging significantly improved in the infarct region after cell therapy compared with placebo in spite of no improvement in global LVEF.[8]

The ASTAMI investigators demonstrated that the improvement in regional LV function (longitudinal strain) by 2-dimensional speckle-tracking echocardiography in the control group was not improved with BMC therapy.[28] Furthermore, circumferential strain from short-axis cardiac magnetic resonance tagging in the last 28 patients (15 BMC) of their trial revealed greater improvement in the control group, similar to the findings of global LVEF.[29] This study highlights the potential benefits of using cMRI for strain measurements because the infarct and border regions can be more accurately delineated by late-enhancing segments on MRI. Overall, the results of regional function analysis have largely correlated with changes in global LVEF. The importance of regional LV function will also be investigated in several upcoming trials by the Cardiovascular Cell Therapy Research Network[30] that has incorporated regional function as part of their primary end points.

Conclusions

This review of cell therapy trials in the setting of STEMI reveals minimal impact of BMC administration on LVEF, volumes, and infarct size when measured by cMRI despite a relatively homogeneous patient population. There remain potentially significant methodological differences between trials including subtle differences in cell processing or timing of cell delivery post STEMI that will need to be investigated in rigorously controlled future studies. The timing of the baseline evaluation of LV function should be rigorously controlled given the rapid improvement in LVEF that may occur during the first week after infarction secondary to the resolution of myocardial stunning or reperfusion injury. Regional measurements of LV function using cMRI or echocardiography should be incorporated into all future cell therapy STEMI studies given the sensitivity of global LVEF to load and hypercontractile regions of remote myocardium.

The development of a composite end point using indices derived from cMRI or regional LV function may provide a better assessment of the benefits of cell therapy. Long-term patient outcome data on mortality, adverse events, prevention of congestive heart failure, and implantable cardiac defibrillator implantation derived from large collaborative trials are needed to support the ongoing use of BMCs after STEMI.

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