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One-Year Follow-up of Intracoronary Stem Cell Delivery on Left-Ventricular Function Following ST-Elevation Myocardial Infarction

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INTRODUCTION

The Timing In Myocardial Infarction Evaluation (TIME)[1] trial assessed whether the timing of stem cell delivery affects the recovery of left-ventricular (LV) function following myocardial infarction. Patients with anterior ST-elevation myocardial infarction (STEMI) who were reperfused with primary percutaneous coronary intervention and stenting and had at least moderate LV dysfunction. (left-ventricular ejection fraction [LVEF] ≤ 45%) were randomized (2:1) to 150 million autologous bone marrow mononuclear cells (BMCs) or placebo with intracoronary delivery performed on Day 3 (n=67) or Day 7 (n=53). At 6 months, no benefit of cell therapy was observed compared to placebo following cell delivery on Day 3 or Day 7. We now report outcomes at 1 year; the collection of clinical endpoint and cardiac magnetic resonance imaging (MRI) data was pre-specified but not the analysis plan.

METHODS

TIME was reviewed and approved by each center's institutional review board with written informed consent collected from all participants. A total of 95 patients (n= 65 BMCs, n= 30 placebo) of the original 112 analyzed at 6 months (n=75 BMCs; n=37 placebo) had analyzable MRI data through 1- year. Reasons for the drop-off between 6-mo and 1-year included implantable cardioverter-defibillator placement (ICD) (3), death (1) loss to follow-up/refused (2), not performed (1) or no-show (10). Follow-up for all patients was completed by November 12, 2012.

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The primary analyses were changes in LVEF and regional (infarct and border zone) LV function between baseline and 6 months by cardiac MRI. Primary and secondary outcomes followed to 1 year are listed in Table 1 and safety outcomes in Table 2. Because an effect of timing was not observed, data are presented as the aggregate of the means of Day-3 and Day-7 groups. Differences in the changes in primary and secondary endpoints between therapy groups and trajectories over time were assessed using repeated measures analysis of variance. Worst case imputation (substitute worse value in the cohort for the missing value) was also conducted. All hypothesis testing was 2-tailed. Results < 0.05 were considered statistically significant. Software analyses was performed with SAS for Windows version 9.3.

RESULTS

LVEF increased from Day-3 to 6-mo in both the BMC (46.2 [(95% CI, 43.9–48.5]) to 50.1 [(95% CI, 47.2–53.0]) %) and placebo groups (46.3 [(95% CI, 43.3–49.3] to 51.5 [(95% CI, 47.5–55.5]) ($p < 0.01$) but did not improve further between 6-mo and 1-year in either group (BMC = 49.5 [(95% CI, 46.5–52.5)%; Placebo = 49.6 [95% CI, 45.8–53.4]%). Regional LV function increased in infarct and border zones between Day-3 and 6-mo in both groups with no further increase between 6-mo and 1-year (Table 1). There were no differences at any time-point between the BMC and placebo groups. Between Day 3 and 1-year, there were increases in LV volumes in both the BMC and placebo groups, with no significant differences between groups (Table 1). The results were unchanged in the worst-case imputation analysis.

Infarct size decreased in the BMC and placebo groups between Day-3 and 6 months with a smaller reduction between 6-mo and 1-year. The reduction in infarct size was accompanied by a similar significant reduction in LV mass through 1-year (Table 1). There were no differences in the reduction in infarct size and LV mass between the BMC and placebo group at any time-points.

There were 2 more repeat infarctions, and 4 repeat-revascularizations and 3 ICD placements (Table 2).

CONCLUSION

The administration of BMCs following moderate to large anterior STEMIs, was not associated with improved recovery of global and regional LV function at 1-year, irrespective of cell delivery at 3 or 7 days post-PCI. The recovery of LV function following STEMI appeared complete by 6-months as no additional improvement in LV function was observed in either group between 6-months and 1-year. Our results do not support the administration of BMCs following myocardial infarction. However, because we were unable to obtain 1-year MRIs on all subjects, the precision of our estimates of change in LV function is reduced.

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Table 1

Baseline, 6-month and 1-year cardiac MRI Results from TIME

	BMC					Placebo							
				CI					CI				
	N	mean	SD	LB	UB	N	mean	SD	LB	UB	P-value*	P-value†	P-value‡
LVEF													
3 day	65	46.2	9.6	43.9	48.5	30	46.3	8.5	43.3	49.3			
6 month	65	50.1	11.8	47.2	53.0	30	51.5	11.2	47.5	55.5	≤0.001	0.20	
1 year	65	49.5	12.3	46.5	52.5	30	49.6	10.7	45.8	53.4	≤0.001		0.30
Regional Infarct Zone (mm)													
3 day	65	3.8	4.9	2.6	5.0	30	4.6	4.6	3.0	6.2			
6 month	65	5.8	6.6	4.2	7.4	30	8.1	6.4	5.8	10.4	≤0.001	0.58	
1 year	65	6.2	5.9	4.8	7.6	30	6.4	5.8	4.3	8.5	≤0.001		0.67
Regional Border Zone (mm)													
3 day	65	16.4	10.2	13.9	18.9	30	14.4	9.8	10.9	17.9			
6 month	65	20.6	11.6	17.8	23.4	30	21.1	13.4	16.3	25.9	≤0.001	0.49	
1 year	65	21.2	12.0	18.3	24.1	30	21.2	13.2	16.5	25.9	≤0.001		0.00
Infarct Size (g)													
3 day	63	44.7	23.1	39.0	50.4	30	46.3	27.4	36.5	56.1			
6 month	63	30.7	15.4	26.9	34.5	30	31.7	20.2	24.5	38.9	≤0.001	0.04	
1 year	63	28.8	15.4	25.0	32.6	30	27.7	17.2	21.5	33.9	≤0.001		≤0.001
LV Mass (g)													
3 day	63	180.4	47.6	168.6	192.2	30	177.3	46.1	160.8	193.8			
6 month	63	156.8	41.0	146.7	166.9	30	161.3	42.6	146.1	176.5	≤0.001	0.00	
1 year	63	148.9	41.8	138.6	159.2	30	151	44	135.3	166.7	≤0.001		0.00
LVEDVI (ml/m2)													
3 day	65	77.1	18.0	72.7	81.5	30	70.5	17.1	64.4	76.6			
6 month	65	86.7	25.0	80.6	92.8	30	80.3	22.8	72.1	88.5	≤0.001		0.14
1 year	65	88.7	25.0	82.6	94.8	30	82.6	22.4	74.6	90.6	≤0.001		≤0.001
LVESVI (ml/m2)													

	BMC					Placebo							
				CI					CI				
	N	mean	SD	LB	UB	N	mean	SD	LB	UB	P-value*	P-value†	P-value‡
3 day	65	41.9	13.5	38.6	45.2	30	38	11.7	33.8	42.2			
6 month	65	44.7	20.3	39.8	49.6	30	40	17.6	33.7	46.3	0.08	0.02	
1 year	65	46.3	21.3	41.1	51.5	30	42.9	18.4	36.3	49.5	0.00		0.02

BMC=bone marrow cells; CI=confidence interval; LB=lower bound; UB=upper bound; LVEF=Left Ventricular Ejection Fraction; LVEDVI=left ventricular end-diastolic volume index; LVESI=left ventricular end-systolic volume index

*vs. Day 3

†1 year vs. 6 month

‡change in the mean value from baseline through six months to one year using a repeated measures mixed model

Table 2

Clinical/Safety Outcomes, Baseline – 1 year

	BMC* (n=79)		Placebo* (n=41)	
Patients with events	18		9	
Deaths	1			
Reinfarctions†	2		3	
Repeat Revascularizations‡	9		6	
Target Vessel		4		4
Non-Target Vessel		5		2
Hospitalization Heart Failure	4		1	
ICD Placements€	4		5	
Stroke	2		2	
Total	**22**		**17**	
CIR	0.228		0.220	

*N=number of patients randomized; BMC=bone marrow cells; ICD=implantable cardiac defibrillator

†=2 new infarctions (1 BMC, 1 placebo)

‡=4 new repeat revascularizations (2 BMC, 2 placebo)

€=3 new ICD (1 BMC, 2 placebo)