The Transendocardial Autologous Cells in Ischemic Heart Failure Trial Bone Marrow Mononuclear Cells (TAC-HFT-BMC) Randomized Placebo Controlled Blinded Study

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Background

Heart failure is in need of new therapies aimed at preventing or reversing cardiac remodeling and at enhancing cardiovascular regeneration. This past decade has seen the emergence of protein, gene, and cell therapies to enhance cardiovascular regeneration.

The clinical safety and efficacy of intramyocardial delivery of autologous bone marrow-derived cells for the treatment of ischemic heart failure and chronic myocardial ischemia have been recently reviewed and the results are overall positive. Significant clinical benefit with a reduction in both mortality and rehospitalization due to heart failure were observed at long term follow-up in patients with chronic ischemic heart disease and heart failure. Significant improvements in heart failure symptoms measured by New York Heart Association Class (NYHA) and in functional capacity measured by left ventricular ejection fraction (LVEF), left ventricular end systolic volume (LVESV), at short-term and long-term follow-up were also observed.

Here, we present the TAC-HFT-BMC study, one of two placebo controlled studies of distinct autologous cell therapies (bone marrow mononuclear cells - BMC or mesenchymal stem cells - MSC) initiated in the TAC-HFT trial[3]. Outcomes of patients randomized to autologous BMC (n=19) and their respective blinded placebo group (n=10) at 12 months from baseline (TAC-HFT-BMC study), incorporating statistical techniques appropriate for missing values are discussed.

Study Endpoints

Primary Endpoint:

Incidence (at one month post-catheterization) of any treatment-emergent serious adverse events (TE-SAEs), defined as the composite of: death, non-fatal MI, stroke, hospitalization for worsening heart failure, cardiac perforation, pericardial tamponade, or sustained ventricular arrhythmias.

Secondary Safety Endpoints:

- AE, SAE, MACE (major adverse cardiac event defined as the composite of death, hospitalization for worsening heart failure, or nonfatal recurrent myocardial infarction)

Secondary Efficacy Endpoints:

- Infarct size, regional wall motion at injection sites, global LV size and function measured by cardiac imaging (CT/MRI)
- Exercise peak oxygen consumption
- 6-minute walk test
- NYHA class
- Minnesota Living With Heart Failure Score

Discussion

- Imputation techniques were used for missing values: Last Observation Carried Forward (LOCF) for missing data; and Worst Observation Carried Forward (WOCF) for missing values attributable to clinically meaningful event (cerebrovascular accident (CVA) in one patient).
- No TE-SAE was observed by day 30 among either the BMC or placebo group.
- At 1-year, the incidence of any serious adverse event (SAE) was 31.6% (95% CI, 12.6-56.6) and 50.0% (95% CI, 18.7-81.3), for the BMC and placebo groups, respectively. No deaths or ectopic tissue formation was reported in either group.
- At 1-year, in the BMC group, no MACE was reported.
- At 1-year, in the placebo group, two out of ten patients experienced clinically meaningful adverse events. One patient experienced a hospitalization for worsening heart failure and one patient experienced a CVA.

TAC-HFT-BMC

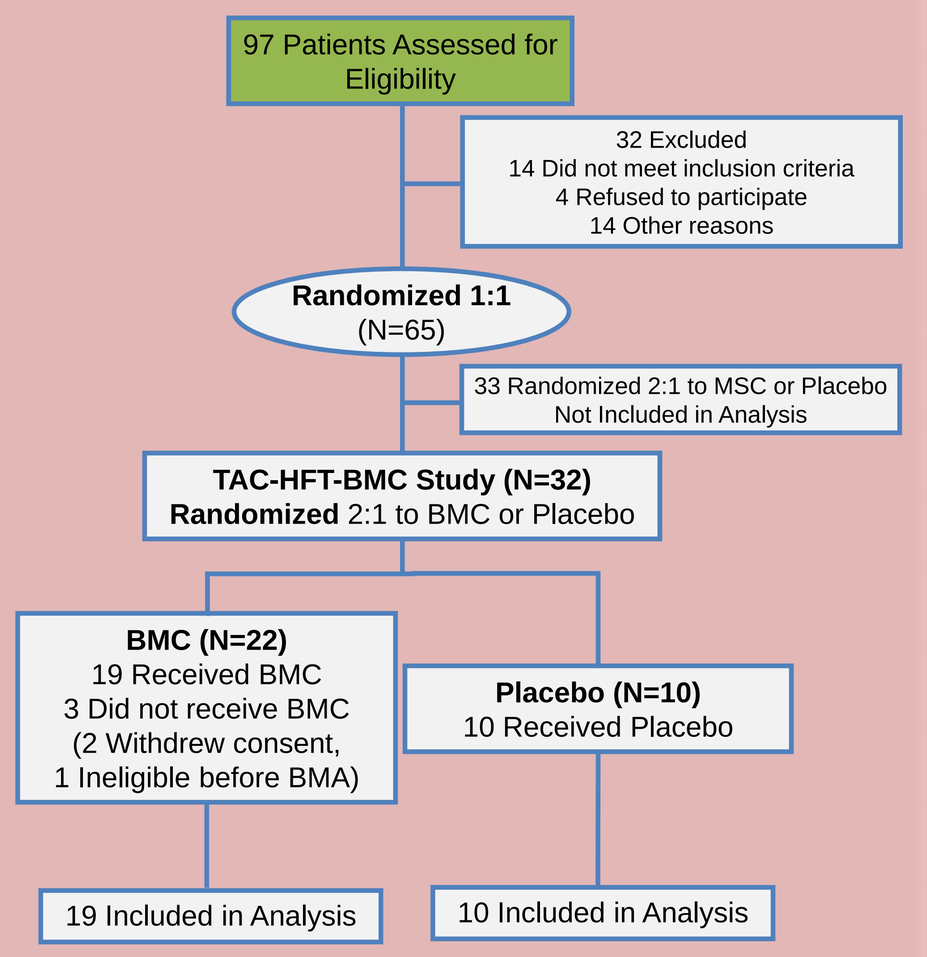
Study Design

Phase I/II, multi-center, randomized (2 Treatment : 1 Placebo Control), double-blind, placebo-controlled study of the safety and efficacy of transendocardial injection of autologous bone marrow mononuclear cells (BMC) versus placebo in patients with chronic ischemic left ventricular dysfunction and heart failure secondary to myocardial infarction.

Treatment Group: 19 Subjects treated with 200 million autologous BMC

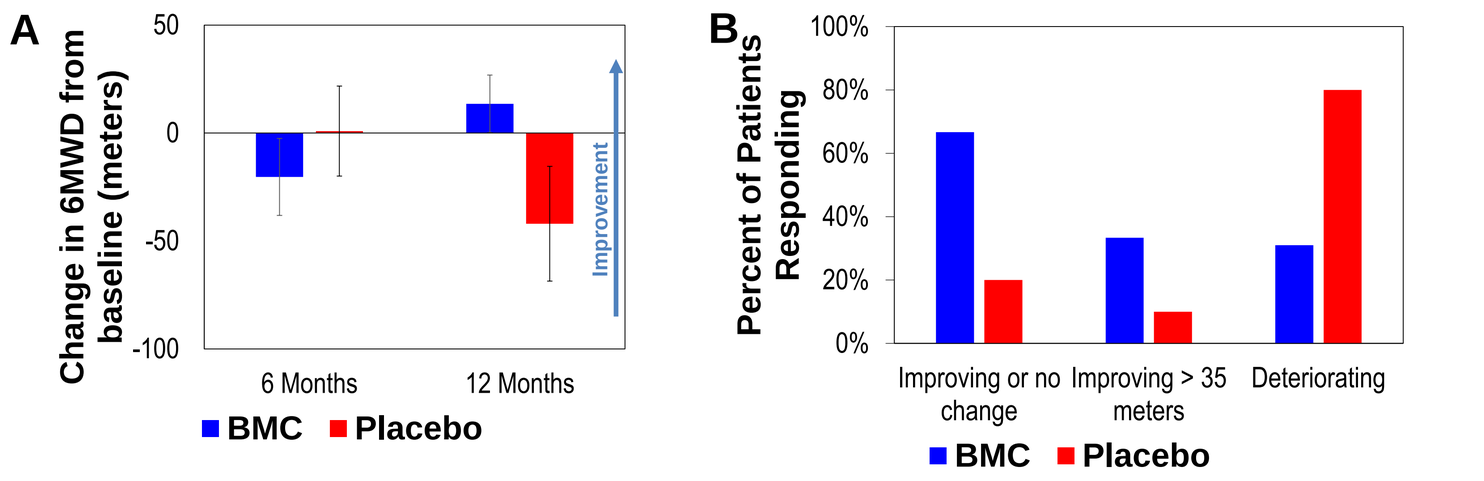
Placebo Control Group: 10 Subjects treated with placebo (phosphate-buffered saline [PBS] and 1% human serum albumin [HSA])

Study Intervention: Autologous BMC or placebo were injected into 10 left ventricular (LV) sites (0.5 ml per injection site) in the infarcted or peri-infarct region with the Helix™ transendocardial delivery system.



Results

Six Minute Walk Distance (6MWD)

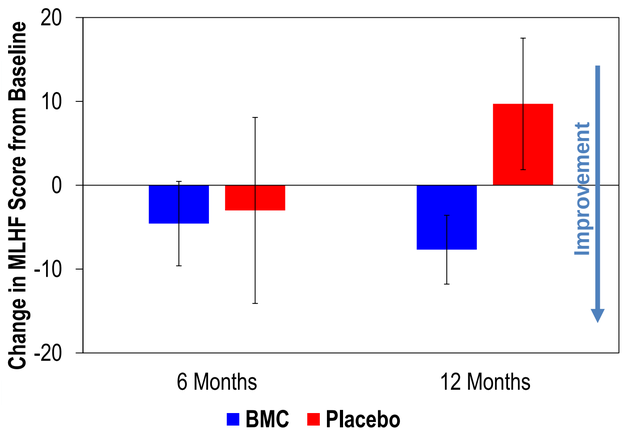


A. Using LOCF and WOCF imputation techniques, mean change for BMC (+14.3m ±SEM) versus placebo (-42.0m ±SEM) at 12 months was statistically significant (p=0.049). **B.** Overall, at 12 Months, the percent of patients improving and improving >35m is greater in the BMC group and the percent of patients deteriorating in the placebo group is over twice that in the BMC group.

Change between BMC and Placebo at 12 M

	No. of Patients			
	Treatment Group		Two-Sample t test	
	BMC (n = 19)	Placebo (n = 10)	P-value	Favors
Study Efficacy Endpoints, No., Mean (SD), [95% CI]				
Six-minute walk distance, m	n = 18, 14.28 (59.66) [-15.39 - 43.94]	n = 10, -42.00 (84.03) [-102.11 - 18.11]	0.049	BMC
MLHF total score	n = 19, -7.68 (17.88) [-16.30 - 0.93]	n = 10, 9.70 (24.80) [-8.04 - 27.44]	0.038	BMC
NYHA Class	n = 19, -0.42 (0.77) [-0.79 - -0.05]	n = 8, -0.25 (1.04) [-1.12 – 0.62]	0.638	BMC
Peak VO_2, mL/kg/min	n = 16, 0.16 (2.27) [-1.05 – 1.37]	n = 10, -0.87 (2.88) [-2.93 – 1.19]	0.321	BMC
FEV1, %	n = 19, -1.68 (12.72) [-7.81 – 4.44]	n = 10, -13.70 (24.91) [-31.52 – 4.12]	0.094	BMC
Cardiac Imaging (MRI/CT) Parameters, No., Mean (SD), [95% CI]				
LV Ejection Fraction, %	n = 17, 0.97 (6.60) [-2.42 – 4.36]	n = 9, -2.38 (7.55) [-8.18 – 3.42]	0.252	BMC
End Diastolic Volume, mL	n = 17, 4.47 (27.36) [-9.59 – 18.54]	n = 9, 51.22 (123.85) [-43.98 – 146.42]	0.143	BMC
End Systolic Volume, mL	n = 17, 3.21 (26.38) [-10.36 -16.77]	n = 9, 47.22 (111.72) [-38.65 – 133.10]	0.129	BMC
Scar mass, g	n = 16, -4.07 (5.40) [-6.95 - -1.20]	n = 9, 2.10 (21.79) [-14.65 – 18.85]	0.286	BMC
Scar size as % of Left Ventricle, %	n = 16, -1.73 (4.49) [-4.12 – 0.66]	n = 9, 0.10 (7.50) [-5.67 – 5.86]	0.451	BMC
Viable Tissue Mass, g	n = 16, 4.02 (11.96) [-2.35 – 10.39]	n = 9, -20.79 (53.41) [-61.84 – 20.27]	0.084	BMC

Minnesota Living with Heart Failure Score (MLHF)



At 12 Months, quality of life measured by Minnesota Living with Heart Failure Score (MLHF) significantly improve in the BMC group (-7.68 ±SEM) versus placebo group (+9.70 ±SEM) (p=0.038). LOCF and WOCF were used to account for missing values.

Conclusion

200 million BMC injected with the Helix transendocardial delivery system were safe in patients with chronic ischemic LV dysfunction. The magnitude of the benefit in the TAC-HFT-BMC results, though modest, are promising and are clinically important when patients are expected to deteriorate. These results have contributed to the design of a recently approved 250-patient randomized controlled pivotal trial of autologous bone marrow mononuclear cells in patients with post myocardial infarction heart failure, the **CardiAMP Heart Failure Trial** (clinicaltrials.gov Identifier **NCT02438306**).

References

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2. Afzal *et al.* Adult bone marrow cell therapy for ischemic heart disease: evidence and insights from randomized controlled trials. *Circ Res.* 2015; 117(6):558-75.
3. Heldman AW et al. Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: the TAC-HFT randomized trial. ***JAMA*** 2014; 311:62-73.

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