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Effect of Transendocardial Delivery of Autologous Bone Marrow Mononuclear Cells on Functional Capacity, Left Ventricular Function, and Perfusion in Chronic Ischemic Heart Failure: The FOCUS-CCTRN Trial

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Abstract

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Context—Previous studies utilizing autologous bone marrow mononuclear cells (BMCs) in patients with ischemic cardiomyopathy have demonstrated safety and suggested efficacy. The FOCUS protocol was designed to assess efficacy of a larger cell dose in an adequately well-powered phase II study.

Objective—To determine if administration of BMCs through transendocardial injections improves myocardial perfusion, reduces left ventricular (LV) end systolic volume, or enhances maximal oxygen consumption in patients with coronary artery disease (CAD), LV dysfunction, and limiting heart failure and/or angina.

Design, Setting, and Patients—This is a 100 million cell, first-in-man randomized, double-blind, placebo-controlled trial was performed by the National Heart, Lung, and Blood Institute-sponsored Cardiovascular Cell Therapy Research Network (CCTRN) in symptomatic patients (NYHA II-III and/or CCS II-IV) receiving maximal medical therapy, with a left ventricular ejection fraction (LVEF)≤45%, perfusion defect by single-photon emission tomography (SPECT), and CAD not amenable to revascularization.

Intervention—All patients underwent bone marrow aspiration, isolation of BMCs using a standardized automated system performed locally, and transendocardial injection of 100 million BMCs or placebo (2:1 BMC: placebo).

Main Outcome Measures—Three co-primary endpoints assessed at 6 months were changes in (a) LV end systolic volume (LVESV) by echocardiography, (b) maximal oxygen consumption (MVO_2), and (c) reversibility on SPECT. Secondary measures included other SPECT measures, magnetic resonance imaging (MRI), echocardiography, clinical improvement, and major adverse cardiac events (MACE). Phenotypic and functional analyses of the cell product were performed by the CCTRN Biorepository lab.

Results—Of 153 consented patients, a total of 92 (82 men; average age, 63 years) were randomized (n= 61 BMC, 31 placebo) at 5 sites between April 29, 2009 and April 18, 2011. Changes in LVESV index, (−0.9 ± 11.3 mL/m^2; P = 0.733; 95% CI, −6.1 to 4.3), MVO_2 (1.0 ± 2.9; P = 0.169; 95% CI, −0.42 to 2.34), percent reversible defect change, (−1.2 ± 23.3; P = 0.835; 95% CI, −12.50 to 10.12), and incidence of MACEwere not statistically significant. However, in an exploratory analysis the change in LVEF across the entire cohort by therapy group was significant (2.7 ± 5.2%; P = 0.030; 95% CI, 0.27 to 5.07).

Conclusions—This is the largest cell therapy trial of autologous BMCs in patients with ischemic LV dysfunction. In patients with chronic ischemic heart disease, transendocardial injection of BMCs compared to placebo did not improve LVESV, MVO_2, or reversibility on SPECT.

Keywords

Chronic CAD; Ischemic Heart Failure; Chronic Angina; bone marrow mononuclear cells; cardiac performance

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Cell therapy has emerged as an innovative approach for treating advanced ischemic heart disease, including patients with refractory angina and/or heart failure. Early clinical studies have been performed primarily using autologous stem/progenitor cells.[1–13] In patients with ischemic heart disease and heart failure, treatment with autologous bone marrow mononuclear cells (BMCs) has demonstrated safety and has suggested efficacy.[10, 14–17]

None of the clinical trials performed to date, however, has been powered to evaluate specific efficacy measures. In addition, autologous cell therapy trials have usually enrolled older patients with acute or chronic left ventricular (LV) dysfunction without evaluation of the impact of these parameters or cell function on clinical outcome. This becomes especially

important when considering that ischemic heart failure has potential to limit the beneficial effects of cellular effects.[6, 18]

The present study (FOCUS-CCTRN) was undertaken by the National Heart, Lung, and Blood Institute (NHLBI)–sponsored Cardiovascular Cell Therapy Research Network (CCTRN)[19] and builds on work from a pilot study in Brazil[10] which in turn led to the first Food and Drug Administration approved randomized phase I trial of autologous BMC therapy in heart failure in the United States (FOCUS-HF).[16] These initial studies showed that transendocardial delivery of BMCs was feasible and appeared safe in patients with chronic heart failure due to multi-vessel coronary artery disease (CAD).[10, 16] Although these preliminary studies also evaluated LV function, perfusion, and functional capacity, a definitive assessment of efficacy was not possible due to the small number of patients. Thus, the present trial was designed as a larger study to investigate the effects of transendocardial-delivered BMCs in patients with chronic ischemic heart disease and LV dysfunction with heart failure and/or angina.[20]

METHODS

Study Design

FOCUS-CCTRN is a randomized, phase II, double-blind, placebo-controlled trial designed to evaluate safety and efficacy of BMCs in patients with chronic ischemic heart disease and LV dysfunction who have no other revascularization options. The primary objective was to determine whether transendocardial administration of 100×10^6 total BMC improves measures of LV performance and perfusion at 6 months compared with baseline levels.

Briefly, clinically stable CAD patients (≥18 years) with left ventricular ejection fraction (LVEF) ≤ 45%, limiting angina (Canadian Cardiovascular Society [CCS] class II to IV) and/or congestive heart failure (New York Heart Association [NYHA] class II–III), a perfusion defect by single-photon emission computed tomography (SPECT), and no revascularization options while receiving guideline-based medical therapy were enrolled.[20]

Study Procedures

The study was conducted at the 5 CCTRN centers; the organizational structure and oversight of the CCTRN have been previously described in detail.[20] The protocol was reviewed and approved by the local institutional review boards at each center. All patients provided written informed consent. Randomization was computer-generated by using variable block sizes of 6 or 9, randomly selected and stratified by center. All randomized patients underwent baseline testing, bone marrow harvest, and automated cell processing performed locally.[20] Patients were randomized in a 2:1 ratio to receive either BMCs or placebo (cell-free) preparation. The cell-containing or cell-free preparation was delivered to viable myocardial regions identified during electromechanical mapping (EMM) of the LV endocardial surface (NOGA®, Biologics Delivery Systems, Cordis Corporation, Diamond Bar, California). All caregivers and patients were blinded to treatment. At 6 months, all baseline testing was repeated in identical fashion.

Baseline assessments have been previously described.[20] Demographic and clinical variables were determined by interview and documented from patient's medical records. Race and ethnicity were recorded as self-described by participants.

Cell harvesting and processing procedures for all CCTRN protocols have been reported in detail elsewhere.[21, 22] Rigorous automated methods for local cell processing were implemented to ensure quality and uniformity of cell preparation. Briefly, approximately 80–100 mL of bone marrow was aspirated from the iliac crest by standard techniques. The

aspirate was processed with a closed, automated cell processing system[21] (Sepax, Biosafe SA).. Composition of $CD34^+$ and $CD133^+$ cells was determined by flow cytometry. After the cells passed stipulated lot release criteria, including viability (>70%) and sterility, randomization was performed by the data coordinating center. Treatment assignment was masked to all but 1 designated cell processing team member at each center not involved in patient care. The target dose for the BMC treatment group was 100×10^6 total BMCs. The BMC final product was suspended in normal saline containing 5% human serum albumin and adjusted to a concentration of 100×10^6 cells in 3 mL distributed into 3 1-ml syringes. The placebo group received a cell-free suspension in the same volume.

Within 12 hours of aspiration, the BMCs or placebo was delivered in 15 separate injections (0.2 mL each) to LV endocardial regions identified as viable (unipolar voltage ≥ 6.9mV) by EMM as described elsewhere.[20] A 2-dimensional echocardiogram was performed immediately after the injection procedure and on the next day before discharge. Serial measurements of biomarkers of CK, CK-MB, and troponin were also obtained. All patients remained in hospital overnight and discharged with guideline-recommended therapy. Patients were examined for safety and efficacy at 6 months. All events deemed to be potential major adverse clinical events (MACE) were assessed by 2 independent cardiologists not affiliated with any clinical site and blinded to treatment assignment. Follow-up for safety continues for up to 12 months with annual phone calls at 2, 3, 4, and 5 years after the intervention.

The CCTRN established a cell Biorepository Core Laboratory to advance the understanding of the relationship between cell product characteristics (composition or phenotype and function) and clinical outcomes.[23] The remaining processed cells (unused cells in the BMC group and all cells from placebo patients) were shipped to the Biorepository core lab with patient consent.

Imaging and Exercise Assessments

Echocardiographic measurements were performed by an Echocardiography Core Laboratory according to published guidelines[24] and included LV end-systolic volumes (LVESV), LV end-diastolic volumes (LVEDV), regional wall motion, and LVEF; myocardial contrast was used to enhance endocardial definition. These were computed by biplane Simpson's rule methodology.[25] LV volume data were normalized for body surface area, and indexed data are presented.

Adenosine myocardial perfusion (SPECT) tests were performed to identity changes in ischemic (reversible) defects from rest and after adenosine infusion over 4 minutes (or if contraindicated, with regadenoson bolus) using standardized protocols. To enhance viability detection on resting images, sublingual nitroglycerin was administered 15 minutes before injection of 99mTc-sestamibi for the resting image. Changes in fixed perfusion defects by SPECT were also measured.

Maximal oxygen consumption (MVO_2)was assessed by using the Naughton treadmill protocol. Blood flow improvement was examined by MRI in patients without MRI contraindications.

Clinical Assessments

Clinical improvement by CCS classification, NYHA class, and change in anti-anginal medications were explored. Serum BNP levels were collected in patients with congestive heart failure, and changes in the levels were assessed at 6 months. MACE was assessed and was defined as new MI, re-hospitalization for PCI in treated coronary artery territories,

death, and re-hospitalization for non-MI acute coronary syndrome or for congestive heart failure.

Sample Size Consideration

The 3 pre-specified primary endpoints—LVESV, MVO_2, and the change in SPECT defect size (6-month follow-up minus baseline)—were evaluated by comparing the change of measure (6 months minus baseline) of the BMC group to the change in the measure of the control group.

For each co-primary endpoint, a sample size was computed based on estimates of the effect size and the standard deviation of the difference from the prior data.[20] Type I error was apportioned at the 0.05 level to be conducted at 80% power with 10% of patients anticipated as lost to follow-up. All testing was 2-sided. The study was designed to detect a mean difference between the groups of 27 mL for LVESV, 5 mL/kg/min for MVO_2, and 10 absolute percentage points for reversible ischemia. To ensure adequate power for each of the 3 endpoints, the sample size was computed for each one, and the maximum sample size was selected.[20] This produced a sample size of 86 subjects, which was administratively increased to 92 patients (31 in the placebo group and 61 in the active group). No type I error adjustment for multiple comparisons was incorporated since this was a phase II study.

Statistical Analyses

All analyses were conducted using Statistical Analysis System (SAS) version 9.2[26] Descriptive statistics for baseline characteristics were generated for (1) demographic variables, (2) medical history, (3) physical examination, (4) laboratory data, and (5) clinical events. Chi-square statistics and Student *t* tests were used to evaluate differences between the treatment arms. General linear modeling techniques assessed effects of treatment on the continuous primary and secondary outcomes of the study. Both unadjusted and baseline covariate-adjusted treatment effects were computed. Dichotomous secondary endpoints (i.e., clinical improvement at 6 months, change in CCS anginal score and NYHA class, decrease in weekly need for anti-anginal medication [nitrates]), were analyzed using Chi-square and Fisher's exact tests. The time-to-event endpoints (i.e., MACE) could not be reliably assessed due to the paucity of events.

Pre-specified subgroup analyses for hypothesis generation examined effects of treatment stratified by age, sex, race, diabetes, serum B-type natriuretic peptide (BNP) levels in patients with heart failure, pre-existing comorbidity, ECFC, and baseline LVEF. Two-sided significance testing was used; P values < 0.05 were deemed statistically significant.

RESULTS

Screening and Enrollment

Screening commenced in March 2009 with 153 patients consented, and between April 29, 2009 and April 18, 2011, 92 patients were randomized. Of the 273 patients screened, most were excluded due to no evidence of reversibility (prior to protocol amendment) or LVEF greater than 45% (Figure 1).[27]

Briefly, this was an older, white male population. Most (76%) patients had an internal cardiac defibrillator (ICD). No statistically significant differences were seen in baseline characteristics comparing the BMC and placebo groups, except for greater ranolazine use in the BMC group, which was consistent with the trend for more patients with CCS class II–IV angina in the BMC group (Table 1). The mean (SD) LVEF on the qualifying

echocardiogram was 32.4 (9.2) in the BMC group and 30.2 (7.8) in the placebo group (P = NS).

Bone Marrow Harvest, Cell Processing, and Delivery

All randomized patients had their marrow processed with Ficoll using the automated Sepax device.[21] The mean volume (SD) of bone marrow harvested was 93.7 (8.3) mL. Time from aspiration to product injection was 8.9 (1.2) hours in the BMC group and 8.6 (2.2) hours in the placebo group.

Cardiac Catheterization, EMM, and Transendocardial Injection

Of the 92 patients randomized, 5 patients were identified as having a lesion suitable for percutaneous revascularization (although no patient had such a lesion identified on the qualifying angiogram). Per protocol, these 5 patients underwent revascularization rather than receive the study product. A sixth patient experienced a limited retrograde catheter-related dissection of the abdominal aorta that precluded study product delivery.

EMM-guided injection of cells or placebo was conducted per protocol in the remaining 86 patients.

Mean viability of the cell product (Trypan blue exclusion) was 98.6% (Table 2). All but 6 BMC-treated patients received the targeted dose of 100×10^6 total nucleated cells, which contained an average of 2.6% $CD34^+$ cells and 1.2% $CD133^+$ cells. Five of these patients had harvests that contained <100 million cells (99.9, 99.6, 99, 80, and 61 million cells). The other patient experienced recurrent VT with hypotension after each injection and received only a small volume of cell product (approximately 13 million cells).

Pre-specified Primary Endpoints

End Systolic Volumes—A total of 54 patients in the BMC group and 28 patients in the placebo group had paired LVESV data at baseline and 6 months (Figure 2). The LVESV index (LVESVI) at baseline was 57.9 ± 26.1 mL/m^2 in the BMC group and 65.0 ± 19.8 mL/m^2 in the placebo group. At 6 months, LVESVI was 57.0 ± 25.5 mL/m^2 in the BMC group and 65.0 ± 23.3 mL/m^2 in the placebo group. The difference in the change in LVESVI between the 2 groups was not statistically significant (change, −0.9 ± 11.3 mL/m^2; P = 0.733; 95% CI, −6.1 to 4.3).

MVO_2—A total of 52 patients in the BMC group and 27 patients in the placebo group had paired MVO_2 data at baseline and 6 months (Figure 2). The baseline MVO_2 was 14.6 ml/kg/min ± 3.8 in the BMC group and 15.3 ml/kg/min ± 4.6 in the placebo group. At 6 months, MVO_2 was 15.0 ml/kg/min ± 4.5 in the BMC group and 14.7 ml/kg/min ± 5.1 in the placebo group. The difference in the change in the BMC group to the change in the placebo group was not statistically significant (change, 1.0 ± 2.9; P = 0.169; 95% CI, −0.42 to 2.34).

Percent Reversible Defect—A total of 52 patients in the BMC group and 25 patients in the placebo group had paired SPECT evaluations at baseline and 6 months (Figure 2). Percent reversible defect during the baseline period was 25.1% ± 27.8 in the BMC group and 11.8% ± 20.4 in the placebo group (P = 0.036). At 6 months, percent reversible defect was 21.3% ± 26.6 in the BMC group and 9.2% ± 9.1 in the placebo group. The difference in the change in the BMC group versus placebo group was not statistically significant (change, −1.2 ± 23.3; P = 0.835; 95% CI, −12.50 to 10.12)..

Pre-specified Secondary Endpoints

SPECT (% Total Myocardium With Defect at Stress)—There were no significant differences in the change between groups over time for percent total myocardial defect (BMC, −1.6 ± 9.7; placebo, −0.7 ± 5.5; change between the groups, −0.9 + 8.6; 95% CI, −5.0 to 3.3), total defect size (BMC, −0.4 ± 7.6; placebo, 1.2 ± 6.4; change between groups, −1.6 ± 7.2, 95% CI, −5.1 to 1.9), or fixed defect size (BMC, 1.2 ±8.7; placebo, 1.9 ± 7.7; change between groups, −0.7 ± 8.4; 95% CI, −4.8 to 3.4).

MRI (Regional Wall Motion and Blood Flow Improvement)—The small number of patients without contraindications for MRI (n=17) precluded performing an informative analysis on the MRI data.

Echocardiography (Regional Wall Motion and LV diastolic dimension)—There were no significant differences between the BMC and the placebo groups in regional wall motion (change, −0.1 ± 0.5; *P*=0.471; 95% CI, −0.30 to 0.14), nor in LVEDVI; (change, 2.5 ± 14.8; *P* = 0.480; 95% CI, −4.4 to 9.3).

Clinical Improvements (NYHA and CCS Classification and Change in Anti-Anginal Medications)—Forty percent of patients in the BMC group and 47% of placebo patients were NYHA class III at baseline. The decrease over time in the percent of patients in the BMC group who were NYHA Class III was statistically significant (p = 0.018); there was no significant difference in the analogous change for the placebo group. However, when between-group analysis was applied, this finding was not statistically significance. Similarly, there were no significant differences in the change in CCS class, serum BNP levels, or decrease in the need for anti-anginal medication between the 2 groups at 6 months (P=0.492, 0.820, 0.284 respectively).

Pre-specified Subgroup Analyses

Subgroup analyses examined the effects of demographics, comorbidities (age, sex, diabetes mellitus, hypertension, angina, and hyperlipidemia), and cell surface markers (CD34 and CD133) on endpoint measures. There were no significant differences.

Non-Prespecified Outcomes

Additional outcomes were examined for exploratory purposes.

2-D Echocardiography (LVEF and Stroke Volume)—The baseline LVEF was available in 54 patients in the BMC group and 28 patients in the placebo group. Baseline LVEF was 34.7% ± 8.8 in the BMC group and 32.3% ± 8.6 in the placebo group. At 6 months, the LVEF increased by 1.4% ± 5.2 in the BMC group; the change in the placebo group was −1.3% ± 5.1. This difference was significant (2.7 ± 5.2%; *P*=0.030; 95% CI, 0.3 to 5.1). Findings for stroke volume were similar, with an increase in BMC patients (2.7 mL ± 12.9) and a decrease in the placebo group (−5.8 mL ± 15.2); this difference was significant (change 8.4 ± 13.7; *P*=0.010; 95% CI, 2.1 to 14.8).

MVO_2 and ECFCs—In an exploratory analysis, BMC therapy was associated MVO_2 improvement for patients with ECFC was greater than the median value of 80 (change 2.5 ± 3.1; 95% CI, 0.16 to 4.88). However the interaction test for this assessment produced a *P* value of 0.914.

LVEF and Cell Phenotypic Markers (CD34 and CD133)—Regression analysis showed that higher CD34+ cell or CD133+ cell counts were associated with greater absolute

unit increase in LVEF. To quantify this relationship, the range of CD34+ was 0.5% to 6.9% (SD=1.2). Assuming that differences of 1.96 SD or 2.4% are more likely due to biologic variability, the effect of differences in CD34+ cell level beyond that expected due to natural variability was examined, using a 3% level to be conservative. Every 3% higher level of CD34+ cells was associated with on average a 3.0% greater absolute unit increase in LVEF in a multiple variable model that included age and treatment as predictor variables. An analogous computation for CD133+ cells (range, 0.1% to 3.6%; SD = 0.62) revealed that every 3% higher level of CD133+ cells was associated with on average a 5.9% greater absolute unit increase in LVEF. The increases were statistically significant ($P = 0.04$ for each), even after adjusting for therapy assignment and age.

Age—The patients were divided based on median age of the population; ≤ 62 years and > 62 years. No statistically significant effect of therapy was seen on the primary endpoints (LVESV, MVO_2, and percent reversibility on SPECT) for age. No significant differences were seen on the secondary endpoints or cell product variables in the subgroup analysis, except for those described below.

When LVEF was assessed, patients ≤ 62 years showed a statistically significant effect of therapy. Patients in the BMC group demonstrated a 3.1% ± 5.2 increase in LVEF from baseline to 6 months, whereas placebo patients showed a −1.6% ± 6.6 decrease. The difference in the change between groups (4.7% ± 5.7) was significant ($P = 0.015$; 95% CI, 1.0 to 8.4).

Safety Outcomes

There were no in-hospital events (other than the dissection noted previously). One patient died 29 days after BMC delivery due to pump failure which was deemed unlikely to be associated with cell therapy. Another patient had a myocardial infarction 61 days after BMC delivery; the infarction did not occur in the targeted injection area, and the patient was discharged 4 days later. There were no rehospitalizations in either group for PCI prior to the 6-month visit. Eight patients (3 BMC and 5 placebo) were re-hospitalized for CHF, with 1 additional patient (BMC) rehospitalized for ACS in this same time frame. One patient (placebo) underwent heart transplantation, and 2 other patients (1 BMC and 1 placebo) had LVAD placements before the 6-month visit.

COMMENT

The CCTRN was developed by the NHLBI to advance cell therapy for patients with cardiovascular diseases by using a collaborative network approach to facilitate larger studies with wide applicability. The FOCUS-CCTRN trial is the first adequately powered study of cell therapy in patients with chronic ischemic heart disease and LV dysfunction (LVEF<45%) to be completed in the USA. We found no significant differences in a priori selected primary endpoints between BMC and placebo-treated patients in this first-in-man study that administered 100 million cells. This protocol randomized 92 patients from a consented cohort of 153 patients, demonstrating the efficiency and expertise of network recruiting as well as the perceived need by the HF community for therapy to address this disease.

Primary endpoints used in previous cell therapy trials of heart failure have been arbitrarily chosen due to lack of sufficient historical data in stem/progenitor cell trials. In these previous studies of patients with ischemic heart disease, both LVEF (echo) and myocardial ischemia (SPECT) were used to measure outcomes of interest and suggested improvement.[5, 28] However, these trials enrolled patients with mostly preserved LVEF (ranging from 48% to 56%). The recently published FOCUS HF trial is one of the first

reported studies of autologous BMC therapy in patients with ischemic heart failure and a low LVEF.[14] That Phase I trial also demonstrated a lack of improvement in the measures that were selected for the current study (LVESV, MVO_2, and SPECT), but at the time of CCTRN-FOCUS design, results of FOCUS HF were unknown. Power calculations for the primary endpoints selected for the current study assumed ambitious improvements in MVO_2 of 5 mL/kg/min, in LVESV of 22 mL, and in reversibility on SPECT of 10% after BMC injections based on a pilot study from Brazil.[10] Since then, exercise training in heart failure patients with low LVEF (HF-ACTION study) resulted in only a 0.6 mL/kg/min improvement in MVO_2 using the same protocol used in FOCUS-CCTRN.[29] Clearly, defining endpoints in this field continues to be a major challenge.

In the present phase II study, exploratory analyses revealed that LVEF was improved in the BMC group compared with the placebo group by 2.7%. Interestingly, this difference is in keeping with results from a previous meta-analysis of BMC therapy in chronic ischemic heart disease and in smaller, individual trials that evaluated BMC therapy in similar patients.[1, 30–32] The modest improvement in LVEF in our study is consistent and may be more meaningful in light of the larger number of patients enrolled.

To examine this finding further, we assessed EF with respect to the bone marrow characteristics of the patient. LVEF improvement correlated with the percentage of $CD34^+$ and $CD133^+$ cells in BMC samples. This correlation was based on a central biorepository assessment of cell surface markers present in the cell product. Evaluating inherent variability in the cell product may provide mechanistic insight into the relationship between cell characteristics and both patient baseline characteristics and clinical outcomes.

Losordo and colleagues[33] recently found a reduction in angina and increased exercise duration with the delivery of autologous $CD34^+$ cells in refractory angina patients who overall had normal LVEF (≥55%). Because our baseline LVEF in BMC-treated patients (32.4%) represented patients with significant LV dysfunction, a meaningful comparison of the results of the 2 studies is difficult. However, both $CD133^+$ and $CD34^+$ cell populations have been shown to give rise to endothelial and vascular progenitor cells and to secrete chemokines and cytokines capable of recruiting cells and promoting cell survival.[34–37] These findings support a model in which $CD34^+$ and $CD133^+$ cells might improve myocardial oxygenation and LV function in areas of ischemia and/or hibernating myocardium; however, further study is needed.

An interesting finding in the FOCUS HF trial[16] was that MVO_2 improved in the younger patients and correlated with cell function in an exploratory analysis. In the present study, MVO_2 improvement correlated with endothelial cell function and warrants further investigation. Additional analyses of cell function will be forthcoming from the CCTRN biorepository and may provide further meaningful correlations with outcome measures. Establishment of the Biorepository Core Laboratory by the CCTRN marks an important step forward in our understanding of the role of cell function in cardiac cell therapy. By providing mechanistic insight, cell phenotypic and functional studies will help in defining meaningful endpoints for future studies and will aid in selecting patients most likely to receive maximal benefits from autologous therapy.

Limitations

Although this study enrolled more patients than in previous HF trials in ischemic heart disease and low LVEFs, the sample size is still relatively small. The sample size chosen required large improvements in selected endpoints to show a significant treatment effect. This choice occurred principally due to the paucity of data available for these evaluations. A large percentage of the patients in our study had contraindications for MRI, thus precluding

a meaningful evaluation of the MRI data due to small numbers. SPECT sestamibi often underestimates myocardial viability and reversibility in patients with multivessel CAD when compared with SPECT thallium or positron emission tomography.[38–41] After approximately 20 months of enrollment in the present study, investigators noted a discrepancy between the amount of reversibility present on baseline SPECT and the subsequent finding of viable myocardium by EMM as well as the presence of angina. Even with minimal reversibility (e.g., 1%) on baseline SPECT sestamibi, a significant amount of myocardial viability was noted on EMM. For this reason and to facilitate enrollment because many patients were being excluded due to the SPECT reversibility criterion, in November 2010 the protocol was amended in the final third period of enrollment to include patients with any perfusion defects (i.e., fixed or reversible). This may have skewed the population to patients with a lesser degree of myocardial viability, limiting the areas suitable for cell injection. Finally, the study size precludes any determination of the effect of therapy on the occurrence of community-wide accepted clinical outcomes (e.g., total mortality), which must be addressed in larger forthcoming studies.

Conclusions

In the largest study to date of autologous BMC therapy in patients with chronic ischemic heart disease and LV dysfunction, we found no effect of therapy on pre-specified endpoints. Further exploratory analysis showed a significant improvement in LVEF associated with treatment. Our findings provide compelling evidence for further studies to determine the relationship between the composition and function of bone marrow product and clinical endpoints. Understanding these relationships will improve the design and interpretation of future studies of cardiac cell therapy.

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Appendix

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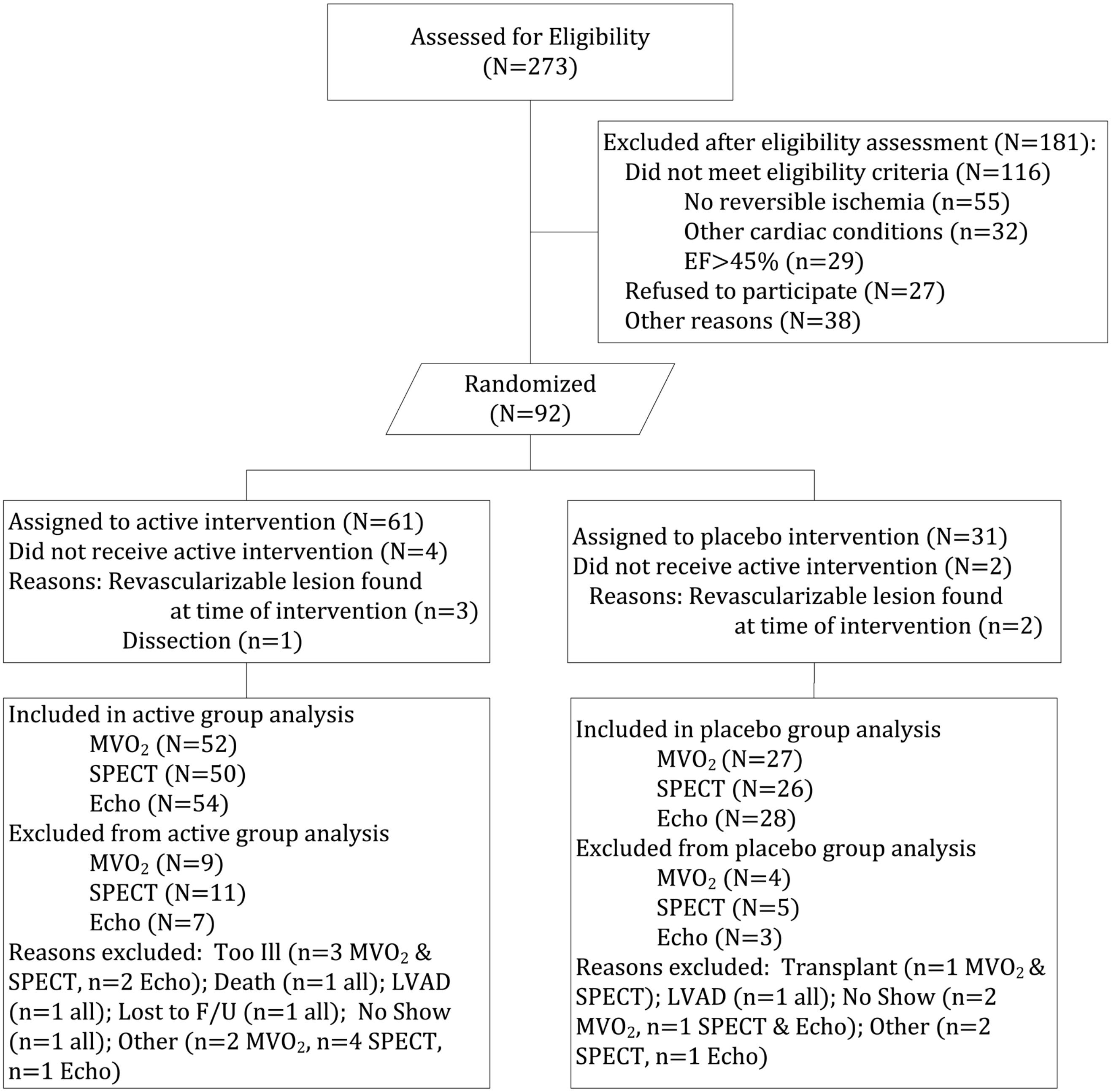

Figure 1.
Flow Diagram of Patients[27]
Abbreviations: EF, ejection fraction; MVO2, maximal oxygen consumption; SPECT, single-photon emission computed tomography; Echo, echocardiography

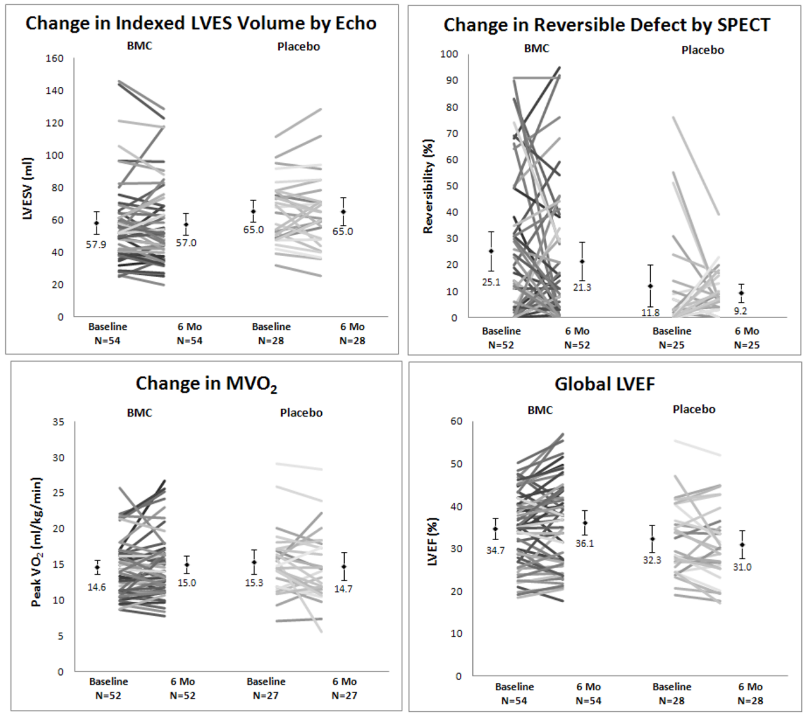

Figure 2. Changes in FOCUS Major Outcomes Over Time by Therapy

Abbreviations: LVESV, left ventricular end systolic volume; Echo, echocardiography; SPECT, single-photon emission computed tomography; MVO2 & Peak VO2, maximal oxygen consumption; LVEF, left ventricular ejection fraction. Solid diamonds represent the means at baseline and 6 months of BMCs and placebo, respectively, and error bars represent 95% CIs each time point. The means are displayed at the bottom of the error bars.

Table 1

Baseline Characteristics

N (%) unless otherwise specified	BMC N=61	Placebo N=31	P-value
Patient Characteristics:			
Age in years, mean (SD)	63.95(10.90)	62.32(8.25)	0.47
Female	8(13.11)	2(6.45)	0.49
Race:			
White	58(95.08)	30(96.77)	1.00
Ethnicity:			
Hispanic	3(4.92)	1(3.23)	1.00
Height in inches, mean (SD)	68.70(3.46)	69.85(3.78)	0.15
Weight inpounds, mean (SD)	203.40(48.89)	222.19(53.84)	0.10
BMI, mean (SD)	30.10(6.14)	31.80(6.60)	0.23
NYHA Classification:			
Class I	6(9.84)	2(6.45)	
Class II	32(52.46)	14(45.16)	
Class III	23(37.70)	15(48.39)	0.59
Class IV	0(0.00)	0 (0.00)	
CCS Classification: (BMC=54, Placebo=25)			
Class I	13(24.07)	10(40.00)	
Class II	24(44.44)	10(40.00)	
Class III	16(29.63)	5(20.00)	
Class IV	1(1.85)	0(0.00)	0.45
BP in mmHg, mean (SD):			
Systolic	120.59(19.69)	122.13(15.78)	0.71
Diastolic	70.95(11.18)	74.77(10.35)	0.12
Heart Rate in BPM, mean (SD)	67.90(10.45)	72.61(13.60)	0.07
median (range)	65.00(51.00–100.00)	70.00(49.00–107.00)	
Qualifying LVEF (echo), mean (SD) (BMC=60)	32.43(9.23)	30.19(7.76)	0.25
Aspiration to Injection Time (hours), mean (SD) (BMC=58, Placebo=29)	8.95(1.18)	8.56(2.22)	0.28
median (range)	9.01(6.52–11.40)	8.98(0.22–11.40)	
Medical History:			
Diabetes	21(34.43)	16(51.61)	0.12
Hypertension	49(80.33)	24(77.42)	0.79
Hyperlipidemia	57(93.44)	29(93.55)	1.00
Angina	21(34.43)	12(38.71)	0.82
Smoking (former or current)	46(75.41)	20(64.52)	0.33
History of MI (BMC=57)	53(92.98)	29(93.55)	1.00
Prior Revascularization	51(83.61)	26(83.87)	1.00
Prior CABG	47(77.05)	25(80.65)	0.79
Number CABG Operations			

N (%) unless otherwise specified	BMC N=61	Placebo N=31	P-value
1	33(70.21)	21(84.00)	
2	13(27.66)	4(16.00)	
3	1(2.13)	0(0.00)	0.39
History CHF	36(59.02)	20(64.52)	0.66
Prior Hospitalization for CHF	14(22.95)	9(29.03)	0.61
Asymptomatic Carotid Disease	11(18.03)	3(9.68)	0.37
History Stroke/TIA	8(13.11)	1(3.23)	0.26
Valvular Heart Disease	18(29.51)	8(25.81)	0.81
Peripheral Vascular Disease	13(21.31)	3(9.68)	0.25
History of Arrhythmia (BMC=56, Placebo=28)	29(51.79)	14(50.00)	1.00
Cardiac Pacemaker	42(68.85)	23(74.19)	0.64
ICD	3(4.92)	2(6.45)	1.00
Dual Chamber pacing	17(18.5)	10(10.9)	0.81
Medications at Time of Randomization:			
ACEi/ARB	37(60.66)	22(70.97)	0.37
Aldosterone Inhibitor	9(14.75)	8(25.81)	0.26
Aspirin/P2 Y12	53(86.89)	29(93.55)	0.49
Betablockers	57(93.44)	30(96.77)	0.66
Coumadin/Warfarin	10(16.39)	4(12.90)	0.77
Digitalis	4(6.56)	4(12.90)	0.44
Diuretics	41(67.21)	23(74.19)	0.63
Nitrates	39(63.93)	18(58.06)	0.65
Statins	44(72.13)	21(67.74)	0.81
Ranolazine	21(34.43)	3(9.68)	0.01
***Laboratory Evaluations*:**			
Hemoglobin in gm/dL, median (range)	14.0 (10.0–16.9)	14.3(12.4–16.6)	0.21
hsCRP in mg/L, median (range) (BMC=54, Placebo=29)	1.4 (0.1–37.0)	1.1 (0.0–86.4)	0.60
GFR in ml/min/1.73m^2, median (range) (BMC=58, Placebo=29)	71.2 (29.6–155.4)	70.1 (30.5–107.3)	0.96
BNP in pg/ml, median (range) (BMC=46, Placebo=23)	132.0 (16.0–545.0)	105.0 (26.0–140.0)	0.68
ProBNP in pg/ml, median (range) (BMC=15, Placebo=8)	833.0 (50.0–9793.0)	828.0 (103.0–5778.0)	0.95

Abbreviations: BMC, bone marrow mononuclear cell, SD, standard deviation, BMI, body mass index (calculated as weight in kilograms divided by height in meters squared), NYHA, New York Heart Association, CCS, Canadian Cardiovascular Society, BP, blood pressure, BPM, beats per minute, LVEF, left ventricular ejection fraction, MI, myocardial infarction, CABG, coronary artery bypass graft, CHF, congestive heart failure, TIA, transient ischemic attack, ICD, implantable cardiac defibrillator, ACEI, angiotensin converting enzyme inhibitor, ARB, angiotensin receptor blocker, hsCRP, high-sensitivity C-reactive protein, GFR, glomerular filtration rate, BNP, brain natriuretic peptide

Table 2

Cell Characteristics

N (%) unless otherwise specified	BMC N=61	Placebo N=31	P-value
Total Nucleated Cells/Product ($\times 10^6$), mean (SD)	99.03(5.58)	100.03(0.18)	0.322
%Viability/product by Trypan blue exclusion, mean (SD)	98.56(1.11)	98.70(0.89)	0.523
%CD34 cells/product, mean (SD) * (BMC=57, Placebo=30)	2.71(1.19)	2.60(0.93)	0.673
%CD133 cells/product, mean (SD) * (BMC=57, Placebo=30)	1.21(0.62)	1.14(0.48)	0.588
Colony Forming Units-Hill/product, mean (SD) * (BMC=55, Placebo=30)	109.41(206.29)	151.33(244.20)	0.404
Endothelial Colony Forming Cells/product, mean (SD) * (BMC=49, Placebo=28)	131.84(164.62)	156.44(240.12)	0.596

*Four patients either declined participation or had insufficient product for the Biorepository.