A double-blind, randomized, controlled, multicenter study to assess the safety and cardiovascular effects of skeletal myoblast implantation by catheter delivery in patients with chronic heart failure after myocardial infarction

Thomas J. Povsic, MD, PhD, FACC,[a] Christopher M. O'Connor, MD, FACC,[c] Timothy Henry, MD, FACC,[b] Andrew Taussig, MD, FACC,[c] Dean J. Kereiakes, MD, FACC,[d] F. David Fortuin, MD, FACC,[e] Alan Niederman, MD, FACC,[f] Richard Schatz, MD, FACC,[g] Richard Spencer, IV, JD,[h] Douglas Owens, RN,[h] Missy Banks, BA,[a] Diane Joseph, BS,[a] Rhonda Roberts, MSPH,[a] John H. Alexander, MD, MHS, FACC,[a] and Warren Sherman, MD, FACC[i] ***Durham, NC; Minneapolis, MN; Orlando, Fort Lauderdale, and Sunrise, FL; Cincinnati, OH; Phoenix, AZ; La Jolla, CA; and New York, NY***

Background We sought to determine the safety and preliminary efficacy of transcatheter intramyocardial administration of myoblasts in patients with heart failure (HF).

Methods MARVEL is a randomized placebo-controlled trial of image-guided, catheter-based intramyocardial injection of placebo or myoblasts (400 or 800 million) in patients with class II to IV HF and ejection fraction <35%. Primary end points were frequency of serious adverse events (safety) and changes in 6-minute walk test and Minnesota Living With HF score (efficacy). Of 330 patients intended for enrollment, 23 were randomized (MARVEL-1) before stopping the study for financial reasons.

Results At 6 months, similar numbers of events occurred in each group: 8 (placebo), 7 (low dose), and 8 (high dose), without deaths. Ventricular tachycardia responsive to amiodarone was more frequent in myoblast-treated patients: 1 (placebo), 3 (low dose), and 4 (high dose). A trend toward improvement in functional capacity was noted in myoblast-treated groups (Δ6-minute walk test of −3.6 vs +95.6 vs +85.5 m [placebo vs low dose vs high dose; $P = .50$]) without significant changes in Minnesota Living With HF scores.

Conclusions In HF patients with chronic postinfarction cardiomyopathy, transcatheter administration of myoblasts in doses of 400 to 800 million cells is feasible and may lead to important clinical benefits. Ventricular tachycardia may be provoked by myoblast injection but appears to be a transient and treatable problem. A large-scale outcome trial of myoblast administration in HF patients with postinfarction cardiomyopathy is feasible and warranted. (Am Heart J 2011;162:654-662.e1.)

Patients with transmural myocardial infarction (MI) are frequently left with considerable myocardial injury due to limitations in the timing and efficacy of thrombolysis and delays associated with primary percutaneous coronary intervention. This has led to increasing numbers of patients with progressive chronic left ventricular (LV) dysfunction and dilation, which accounts for a large component of the growing prevalence of heart failure (HF), one of the most burdensome medical conditions.[1]

Numerous angiogenic and cellular agents have been studied in patients with refractory angina pectoris, targeting regions of ischemic and viable myocardium.[2-4] However, novel regenerative strategies for patients with chronic ischemic HF and scarred myocardium are few.

From the [a]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, [b]Minneapolis Heart Institute, Minneapolis, MN, [c]Florida Hospital Center and Cardiovascular Institute, Orlando, FL, [d]The Christ Hospital Heart and Vascular Center, Cincinnati, OH, [e]Mayo Clinic Hospital, Phoenix, AZ, [f]Jim Moran Heart and Vascular Research Institute, Fort Lauderdale, FL, [g]Heart, Lung and Vascular Center, The Scripps Clinic, La Jolla, CA, [h]Bioheart Inc, Sunrise, FL, and [i]Center for Interventional Vascular Therapy, Columbia University Medical, New York, NY.

Submitted February 2, 2011; accepted July 17, 2011.

Reprint requests: Warren Sherman, MD, Columbia University Medical Center, 173 Ft Washington Avenue, HC2-610, New York, NY 10032.
E-mail: ws2156@columbia.edu

0002-8703/$ - see front matter

doi:10.1016/j.ahj.2011.07.020

The induction of angiogenesis alone is unlikely to restore function to areas of ventricles depleted of cardiomyocytes.[5] Moreover, vascular progenitors are largely intolerant of the levels of hypoxia found in myocardial fibrosis and do not undergo myogenic transdifferentiation in numbers sufficient to generate contractile tissue.[6,7] Therefore, myocyte replacement relies on the availability of cell sources with high degrees of myogenic potential.

Few populations of adult stem cells containing a preponderance of myogenic phenotypes are available for clinical study. Resident cardiac stem cells,[8-10] derived from autologous myocardium, are a promising population, although hampered by low cell yields using current isolation and expansion techniques. Skeletal myoblasts, although not cardiomyocyte progenitors, are well suited for large clinical trials, given their ease of procurement and scale-up and intrinsic resistance to hypoxic conditions. In models of chronic myocardial injury, myoblasts form grafts that are fatigue resistant, contribute to cardiac workload, and improve hemodynamics.[11-14] Early-phase human studies of myoblasts have been encouraging with regard to clinical effects and safety.[15-19] These studies have been limited by concomitant surgical revascularization[20] or the lack of suitable placebo control groups.[21,22]

MARVEL was designed as a 330-patient randomized, placebo-controlled, phase IIb to III trial to assess the safety and clinical efficacy and dose response of percutaneous myoblast administration in a population with HF. However, limited financial resources required suspension of enrollment. With enrollment suspended and follow-up on the first cohort of patients (n = 21) complete, the steering committee recommended partitioning MARVEL into a pilot phase, MARVEL-1, with the goal of informing the future design of a larger definitive MARVEL trial.

We report the safety and preliminary efficacy results of the MARVEL-1 population. MARVEL-1 represents the first randomized placebo-controlled trial of catheter-based myoblast administration as a sole intervention in patients with post-MI cardiomyopathy and HF. Although no longer powered to achieve MARVEL's primary outcomes, MARVEL-1 provides important data pertinent to cell-based therapies and offers insights into the conduct of a randomized, blinded, placebo-controlled cell therapy trial.

Methods

Study population and design

MARVEL-1 was conducted in 6 US centers between October 2007 and September 2008. Follow-up was completed in April 2009. The protocol was approved by the institutional review board of each institution, and all patients provided written informed consent. The MARVEL trial was funded by Bioheart Inc (Sunrise, FL). In addition, Dr Povsic was the recipient of a Duke Pepper Older Americans Independence Center Research Career Development Program in Aging Research (5P30AG028716) Award.

Eligibility criteria

Patients aged 18 to 80 years with New York Heart Association (NYHA) class II to IV HF and impaired LV systolic function (ejection fraction <35%) were eligible if they were stable with respect to symptoms (>60 days on optimal medications) and ventricular arrhythmias (>90 days without ventricular fibrillation or sustained ventricular tachycardia [VT]) after insertion of an automatic implantable cardioverter-defibrillator (ICD). Patients were required to have structural characteristics of a chronic infarction on screening stress echocardiography with defined akinetic areas of infarction involving the anterior, lateral, posterior, or inferior walls suitable for transendocardial injections (wall thickness >5 mm). Patients were excluded if their primary symptom was angina, if they had a recent MI or percutaneous coronary intervention (<90 days), if they had recent coronary artery bypass graft surgery (<150 days), or if they had recent cardiac resynchronization therapy (<180 days). Patients with planned revascularization and primary myocardial or moderate-to-severe valvular disease were also excluded.

Required parameters of HF included the following: Minnesota Living With HF (MLWHF) questionnaire score ≥20, 6-minute walk test (6MWT) ≤400 m, and serum brain natriuretic peptide (BNP) levels ≥100 pg/mL.

Noncardiac causes for exclusion included the inability to perform a 6MWT (claudication, pulmonary function, or other diseases limiting mobility); serum creatinine >2.5 mg/dL; anemia, infection with human immunodeficiency virus, human T-cell lymphotropic virus, hepatitis B or C, or active cytomegalovirus; or any illness that might reduce life expectancy to <1 year.

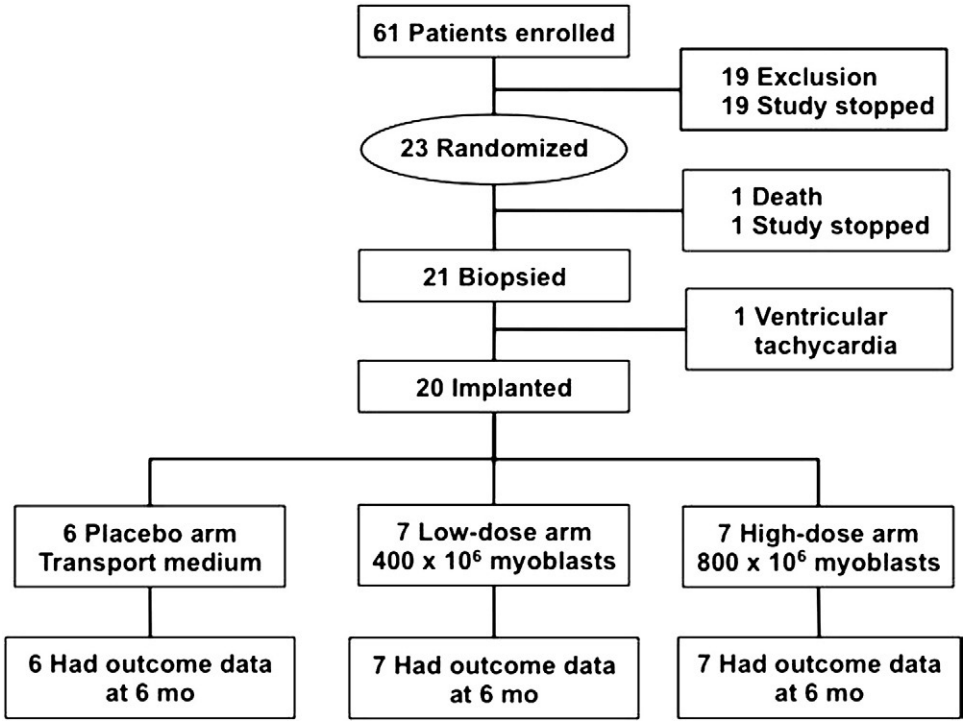
Randomization, cell preparation, and study intervention

After enrollment, patients were randomly allocated by an interactive voice response system (Interactive Clinical Technologies, Yardley, PA) equally to 1 of 3 groups: placebo, low-dose myoblast, or high-dose myoblast (400×10^6 or 800×10^6 myoblasts). All subjects underwent open surgical biopsies (≥10 g) of the thigh muscle by a surgeon blinded to treatment assignment. Biopsy specimens were sent to a centralized good manufacturing practice facility (Bioheart, Weston, FL) where culture expansion was performed on biopsies from low-dose and high-dose groups only. Study agents consisting of 4 to 5 mL of transport media (Hypothermosol; BioLife Solutions, Bothell, WA) alone (placebo group) or suspensions of 400×10^6 myoblasts (low dose) or 800×10^6 myoblasts (high dose) in transport media were sent to the clinical sites between 16 and 20 days postbiopsy.

All patients underwent electromechanical mapping of the left ventricle[20,21] and image-guided implantation (NOGAStar and MyoStar, Diamond Bar, CA), consisting of 16 infarct-targeted injections (0.25 mL/injection) of study product. All injections were performed using the MyoStar catheter injected into the LV wall at half the measured thickness as determined by echocardiography. Measured unipolar voltage at the injection site was to be <7 mV. Due to slight differences in turbidity of the 3 study preparations, the operative team had no further contact with subjects after the procedure. A separate blinded investigator team was responsible for all patient contact and follow-up.

Before discharge and at prespecified intervals through 180 days, patients underwent assessments of clinical status, cardiac biomarkers, 6MWT, MLWHF questionnaire, ICD interrogation,

Figure 1



Patient flow diagram.

dobutamine stress echocardiography, and multiple-gated acquisition (MUGA) scans.

Outcome measures

The primary safety outcome was the incidence of serious adverse events at 6 months, including death, MI, rehospitalization, and ventricular arrhythmia. All arrhythmic events were adjudicated at the Duke Clinical Research Institute (Durham, NC) by physicians unaware of treatment group.

The prespecified coprimary efficacy outcomes were changes in 6MWT and MLWHF scores between baseline and 6 months. Prespecified secondary outcomes included changes in 6MWT and MLWHF scores at 3 months; NYHA HF classification at 3 and 6 months; resting ejection fraction by MUGA at 3 and 6 months; LV volumes, regional wall motion, and mitral regurgitation by echocardiography; serum BNP levels at 6 months; and readmission and cause-specific readmission rate, time to death or readmission, and total days alive outside of the hospital. Multiple-gated acquisition and echocardiography images were blindly assessed by a core facility (Northwestern University, Chicago, IL), and blood levels (BNP, cardiac enzymes) were assessed at a central laboratory (Esoterix, Austin, TX).

Table I. Baseline characteristics

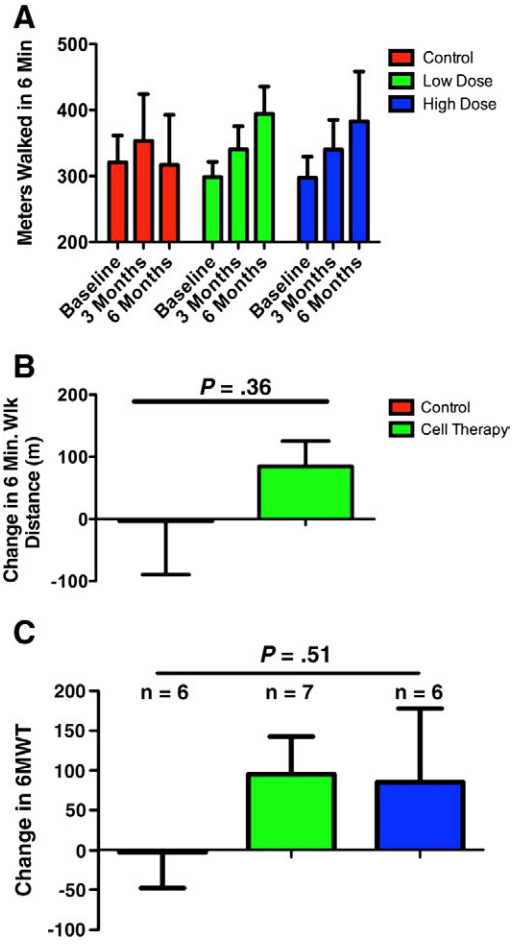
	Placebo (n = 6)	Low Dose (n = 7)	High Dose (n = 7)	*P*
Age (y), median (25th, 75th)	63 (43, 68)	73 (63, 77)	74 (58, 79)	.20
White	100%	100%	100%	NA
Male	100%	100%	85.7%	1.0
NYHA class II	50%	14.3%	42.9%	.51
Angina	33.3%	42.8%	0%	.197
Diabetes mellitus	50%	57.1%	28.6%	.64
Interval since MI (y)	7.9	12.3	15.2	.59
CABG or PCI	16.7%	85.7%	71.4%	.054
VT	16.7%	14.3%	28.6%	1.0
PAD	0%	0%	28.6%	.30
Ejection fraction (%), mean ± SD	23.3 ± 7.6	25.8 ± 2.8	26.2 ± 7.8	.76
6-MWT (m), mean ± SD	320.5 ± 100.1	303.6 ± 73.4	298.1 ± 60.5	.87
MLWHF score, mean ± SD	60.8 ± 23.1	38.6 ± 7.7	54.6 ± 22.5	.12

CABG indicates Coronary artery bypass grafting; *PCI*, percutaneous coronary intervention; *PAD*, peripheral arterial disease.

Statistical analysis

Two-tailed statistical analyses were performed using SAS software, version 8.2 (SAS Institute Inc, Cary, NC). Baseline patient characteristics were summarized using means with standard deviation for continuous variables and frequencies and percentages for categorical variables. All eligible patients received assigned therapy, and an intention-to-treat analysis was used. Comparisons of the 2 study groups with respect to the change from baseline in the primary efficacy end points were performed using Wilcoxon rank sum tests. The prespecified statistical

Figure 2



A, Six-minute walk distance at baseline and at 3 and 6 months in control, low-dose, and high-dose groups. **B**, Change in 6-minute walk: cell therapy vs control subjects. **C**, Change in 6MWT in control, low-dose, and high-dose groups.

analysis plan indicated that patients lacking follow-up data were to be removed from the analysis; however, sensitivity analyses were performed to determine the effect of an extreme value substitution as well as carried-forward approach on outcomes.

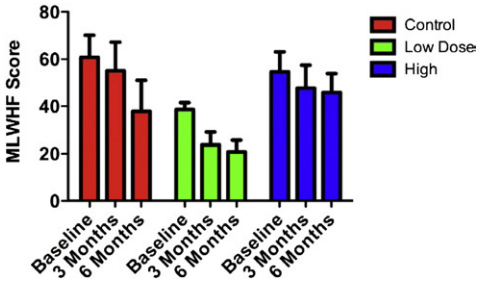
The executive committee was responsible for all decisions regarding study design and conduct. An independent data and safety monitoring board assessed safety data as they became available. After randomization of the ninth subject, unblinded data were provided to the data and safety monitoring board as a result of a perceived excess in VT. Recommendations regarding study continuation, protocol amendments, and methodological changes were conveyed to the executive committee.

Results

Baseline clinical and demographic characteristics

A total of 61 patients (Figure 1) were enrolled in MARVEL; 23 patients were randomized before suspension of enrollment. Of these, 2 did not undergo muscle biopsy (1 death, 1 withdrawal). One randomized patient was excluded due to VT and ICD discharge in the period between muscle biopsy and planned cell administration and was not analyzed as part of the MARVEL-1 treatment group. The remaining 20 patients, randomized between October 2007 and October 2008, formed the MARVEL-1 study population.

Figure 3



Change in MLWHF questionnaire score during the follow-up. Control, low-dose, and high-dose groups.

Patient characteristics among treatment groups (Table I) were reasonably well matched with respect to sex, race, and cardiac risk factors. The baseline ejection fraction (mean, 25.2% ± 6.4%), 6MWT distance (mean, 307 ± 74 m), and MLWHF score (mean, 50.8 ± 20.3) attest to the significant LV dysfunction and symptoms in these patients. Myoblast-treated patients were older, had a higher degree of prior revascularization, and had more HF symptoms as measured using the MLWHF score.

Successful skeletal muscle biopsies were taken from all patients. Specimens were of comparable weight across treatment groups and gave rise to cell yields that exceeded target doses for both myoblast groups. Cell viability (>99%) and myotube formation (>95%) were uniformly high in all cultures. Catheter-based image-guided study injections were accomplished in 20 patients, each receiving the full 4 mL of product allocated. All patients underwent successful electromechanical mapping using the NOGA-XP system, with delivery of cells using the MyoStar catheter (each patient received all 16 injections of 0.25 mL each).

Efficacy outcomes

Clinical follow-up was available at 6 months for all 20 patients treated. For evaluation of efficacy, MLWHF scores were available in 19 patients and 6MWT results in 17. One patient (high-dose group) required cardiac transplantation at 3 months, and 2 patients were unable to complete 6MWT due to orthopedic conditions that arose between 3 and 6 months.

Table II. Events listed by treatment group

	Placebo		Low Dose		High Dose	
	Patients	Events	Patients	Events	Patients	Events
Sustained VT	1	1	3	3	3	4
Symptomatic bradycardia	0	0	0	0	1	1
HF	0	0	2	2	1	1
Respiratory failure	0	0	1	1	0	0
Chest pain	2	4	0	0	0	0
Other CV	0	0	0	0	1	1
Other non-CV	1	3	1	1	1	1
Total	4	8	6	7	4	8

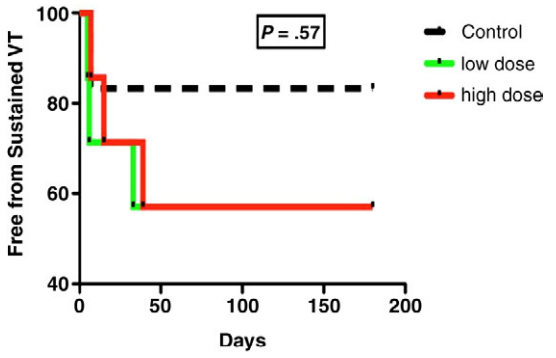
CV indicates Cardiovascular.

The primary efficacy outcome of the 6MWT demonstrated numerical improvement at 6 months (Figure 2A and the online Appendix for individual patient data). Although placebo patients exhibited essentially no change (−3.7 ± 86 m), low-dose and high-dose myoblast groups experienced an increase of nearly 90 m (+95.6 ± 47.2 and +85.5 ± 82.1 m) (Figures 2B and C). Using a repeated-measures test to assess change in walking distance over time, an increase in 6MWT distance of 48.8 m was observed in the combined myoblast group ($P < .05$, 95% CI 7.06-90.6 m) as opposed to 8.8 m in those given placebo ($P = .8$, 95% CI −54.2 to 70.6 m), with a difference between the control and myoblast groups of 40.8 m ($P = .28$, 95% CI −35.7 to 117.4 m). In a sensitivity analysis using a carried-forward (prespecified) or a worst-case approach to determine the effect of the patient in the high-dose group who underwent cardiac transplantation, the results in the high-dose group were more muted (high-dose group +73.3 ± 79.4 m [carried forward] or +31.3 ± 252 [worst case]).

Improvements in MARVEL's coprimary end point (MLWHF score) were noted in all treatment groups, with average changes of −22.8 ± 9.7, −17.7 ± 4.3, and −3.8 ± 7.6 points in placebo, low-dose, and high-dose groups, respectively (Figure 3) ($P = .6$). The combined cell-treated patients showed an improvement of −11.3 ± 16.3 ($P = .3$ for comparison with control). More than 2 of every 3 patients reported gains in both MLWHF score and NYHA class at the 6-month follow-up, with no difference between the myoblast and placebo groups.

The effect of myoblast administration on LV function was an important component of the MARVEL study design. Six-month data were available for ejection fraction assessment by MUGA in 17 patients and for ejection fraction, wall motion, and LV dimension evaluation by echocardiography in 16 patients. There were no differences observed among the treatment groups in any of these variables. Brain natriuretic peptide levels were available in 15 patients at the 6-month follow-up. In control patients, BNP increased by 275 pg/mL over baseline measurements, whereas smaller changes were observed in both low-dose (−82 pg/mL) and high-dose (143 pg/mL) myoblast groups.

Figure 4



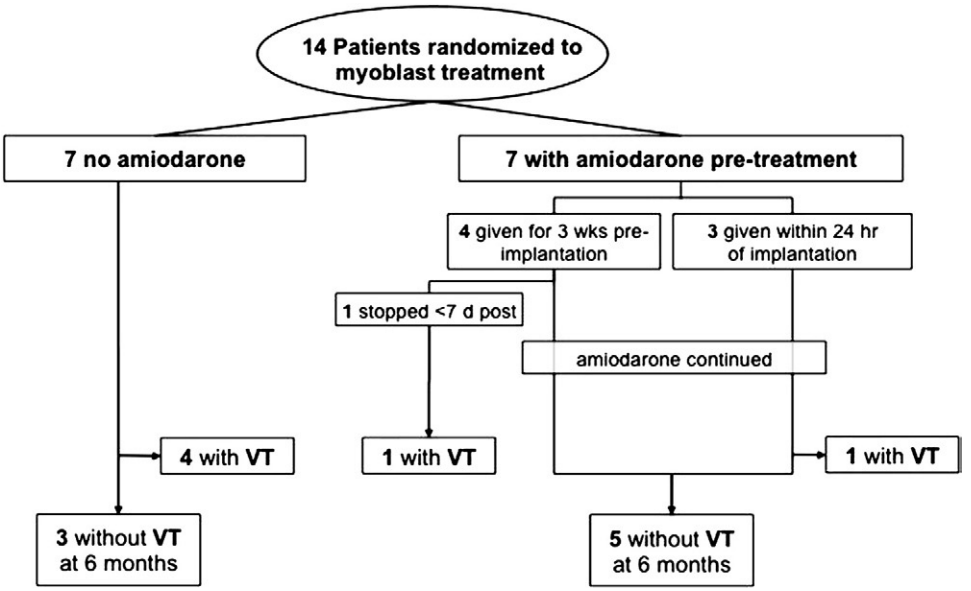
Freedom from sustained VT according to treatment group.

Safety analysis

The number of patients experiencing adverse events and the total number of events were similar among the 3 groups (Table II). However, the frequency of VT requiring treatment was higher in the myoblast groups than in the control group, whether categorized by numbers of affected patients (3/7 after low-dose or high-dose vs 1/6 after placebo) or by the total number of treated events (39 vs 18 vs 3 in low dose [7 patients], high dose [7 patients], and placebo [6 patients]). Kaplan-Meier survival curves for freedom from VT reflect the higher level of VT in the myoblast-treated patients (Figure 4). All VT events occurred between 5 and 39 days of implantation, with no events during or within 24 hours of injection of myoblasts. All patients experiencing VT were hospitalized and placed on amiodarone therapy with resolution of their arrhythmias.

After a summary of blinded VT events was reported to clinical sites, the use of prophylactic amiodarone was left to the discretion of the investigators. Of 11 subsequently

Figure 5



Relationship between amiodarone therapy and VT events in myoblast-treated patients.

enrolled patients, 8 were placed on amiodarone, although timing and dosing varied. We performed a patient-by-patient analysis to determine the association between prophylactic amiodarone and subsequent ventricular arrhythmias (Figure 5). Among 14 patients randomized to myoblast therapy, 7 received no prophylactic amiodarone. Of those 7, 4 developed postinjection VT requiring ICD therapy. Three patients were either started on amiodarone at the time of cell implantation (n = 2) or discontinued the medication after cell implantation (n = 1). Two of these 3 patients developed VT in the postinjection period. Four patients were started on amiodarone at the time of peripheral muscle biopsy, allowing a 3-week oral loading period before cell implantation. No VT was observed in these patients.

Discussion

Major findings

MARVEL is the first blinded placebo-controlled trial assessing the safety and efficacy of percutaneous myoblast administration for patients with advanced symptoms of HF due to transmural infarction. Due to a severe curtailment in enrollment because of financial constraints, conclusions from MARVEL-1 are more limited than initially designed. However, our observations from MARVEL-1 can be briefly summarized: (1) sustained VT requiring intervention was notable and more frequent in myoblast-treated patients, though not statistically significant; (2) enrollment was brisk, even with an invasive control group; (3) logistic problems were very few, despite the complexity of the study; and (4) some improvements in objective functional capacity were observed, although these were not replicated in symptom-driven assessments.

Safety: VT

The association of myoblast administration with VT is unresolved, with data from preclinical and clinical studies that support[16,20,23] or question[22,24,25] a causal relationship. The picture is blurred further by variable application of prophylactic antiarrhythmic therapy before or upon study enrollment.[20] We minimized background noise by excluding patients with recent VT, thereby preselecting a population in whom VT requiring therapy before enrollment was low and to maximize patient safety by requiring prior ICD implantation.

Ventricular tachycardia (on a per-patient and per-episode basis) was more frequent in the myoblast groups. Among patients randomized to myoblast therapy not treated with prophylactic amiodarone therapy, >50% required automatic ICD therapy. Communication of observed events in the first 9 patients in MARVEL-1 led to institution of empiric amiodarone administration in most patients subsequently enrolled. No ventricular arrhythmias were observed in patients in whom oral amiodarone was begun 2 to 3 weeks before myoblast administration and maintained without interruption for the following 5 weeks. Amiodarone therapy was empirically discontinued after a 3-month period, and no further VT events were noted during the additional follow-up period. Our limited data demonstrating the effectiveness of this strategy and the time

dependency (<39 days postinjection) of these events suggest that a focused period of surveillance and treatment with amiodarone may effectively suppress VT during this risk period.

Prophylactic amiodarone may carry some risk. Reassuringly, meta-analyses of amiodarone in this population with advanced HF suggest no mortality risk,[26] and the risks of prophylactic amiodarone in another patient cohort did not appear excessive.[20] In addition, amiodarone might theoretically increase defibrillation thresholds, making automatic ICD therapy less effective. It may be reasonable to exclude patients with known high defibrillation thresholds from such therapy. Whether these safety concerns are outweighed by potential benefits will require adequately powered trials to fully define the risk/benefit ratio of percutaneous myoblast delivery.

Three patients in the myoblast-treated groups experienced worsening HF. We were unable to identify specific causes of these events and can only speculate as to whether disease progression, study injections, or other processes were at play. More definitive trials would be required to do so in this high-risk patient population.

Efficacy

MARVEL-1 is limited from demonstrating significance in original efficacy end points by its small size and wide standard deviations. When compared with placebo, myoblast therapy was associated with sustained (6 months) improvements in 6MWT distance of >90 meters, a clinically meaningful improvement if replicated in larger studies. Subjective quality of life measures improved among all groups with large fractions of control patients reporting beneficial changes in NYHA class (67%) and MLWHF score (83%) after placebo injection. This distinguishes MARVEL-1 from its predecessors, SEISMIC[21] and CAUSMIC,[22] both open-label studies with medically treated control groups, in which fewer control patients (57%-58%) improved with respect to subjective parameters, and suggests that demonstrating improvements in subjective parameters will be difficult in truly blinded studies in this field. Objective changes in 6MWT distance increased in similar numbers of control patients in all 3 studies (~30%), suggesting that functional tests are less likely to be influenced by patient blinding. Findings from blinded placebo-controlled studies in patients with chronic myocardial ischemia[27-29] support observations from MARVEL-1 regarding the benefits of cell administration on objective assessments of patient function.

Dose response

When MARVEL was designed, there were little data to guide dose selection of myoblast therapy, although the MAGIC trial suggested improved efficacy with higher myoblast dosing.[2] In addition, the reliability of achieving the high dose of 800×10^6 cells was unproven. MARVEL was designed as a phase IIb/III study to determine the relationship between dosing and outcomes in a definitive manner. Unfortunately, given the final enrollment, no conclusions about dose response can be made.

Uniqueness of MARVEL in the cell therapy arena

Previous studies have established the feasibility and potential efficacy of myoblast administration by surgical and transcatheter techniques in low-to-moderate doses for patients with chronic postinfarction HF. MARVEL was designed to advance the strategy of cardiac repair with myogenic precursors to the phase III clinical trial, incorporating design elements relevant to this challenging population of patients. MARVEL attempted (1) to assure blinded enrollment into active agent and placebo groups to allow definitive determination of safety and efficacy, (2) to reveal mechanistic insights through multiple-dose administration and assessment tools, and (3) to provide clinical relevance through the participation of many investigative centers and the uniform application of operational standards (cell production and delivery and outcomes monitoring).

MARVEL-1 achieved several important goals. Recruitment into a blinded, placebo-controlled study testing an autologous cell line requiring harvest was rapid, attesting to the perceived clinical need for therapy for patients with congestive HF due to transmural infarction. In all patients eligible for study injection, cell procurement and expansion and catheter-based intramyocardial delivery were successful and seamless, without untoward procedure-related events. MARVEL is the first study to use high-dose, low-volume myoblast preparations suitable for transcatheter delivery.

The evolution and conduct of the MARVEL trial, its transition to MARVEL-1, and the data derived from this experience are valuable to the progress of stem cell–based cardiovascular repair. Skeletal myoblasts, among the most extensively studied of adult stem cells, are the only myogenic progenitor population targeted to patients with infarcted scarred myocardium. MARVEL was scaled back for reasons highly pertinent to contemporary clinical biosciences—achieving an appropriate balance between the cost of a study and its imperative to incorporate crucial measures of safety and efficacy outcomes. The inability to do so presents a serious obstacle to progress in the still nascent field of stem cell–based repair.

Despite its lack of power to achieve MARVEL's principal goals, MARVEl-1, with its blinded placebo-controlled design, signals the feasibility of performing large-scale clinical trials with autologous skeletal myoblasts. Perhaps more importantly, the MARVEL program set a methodological foundation for the conduct of double-blind, placebo-controlled studies in cardiovascular cell therapy, maintaining a blinded placebo group with the inclusion of cell harvesting and placebo injection procedures.

Conclusions

MARVEL-1, an initial phase of a planned broader MARVEL program, demonstrated the feasibility of conducting blinded, placebo-controlled studies assessing the efficacy of percutaneous implanted cell therapy product (myoblasts) on objective and subjective parameters. Percutaneous myoblast injection was associated with numerical improvements in 6MWT distance but also with a higher short-term incidence of amiodarone-responsive VT. Our results might be used to guide future investigations in cell therapy for cardiovascular disease, especially in those using myogenic progenitors, and suggest that cautious research for patients with advanced symptoms and lacking other approved or experimental options is warranted to improve functional capacity.

Acknowledgements

Executive Committee: W. Sherman (Chair), T. Henry, T. Povsic, and C. O'Connor.

Data Safety Monitoring Board: University of San Francisco, Veterans Hospital, San Francisco, CA: B. Massie (Chair); University of California, San Diego, CA: B. Greeberg; University of California, San Francisco, San Francisco, CA: Y. Yeghiazarians; Duke University Medical Center, Durham, NC: J. Daubert and V. Hasselblad; University of Wisconsin, Madison, Wisconsin: D. DeMets; Hannover Medical School, Hannover, Germany: H. Drexler.

Role of the sponsor: Bioheart, Inc, contributed to the design of the study. The sponsor had no role in the conduct of the study or the collection, management, analysis, and interpretation of the data and in the preparation and/or approval of the manuscript.

Study sites, principal investigators, and primary study coordinators: Minneapolis Heart Institute, Minneapolis, MN: T. Henry and Patti Mitchell; Florida Hospital Center, Orlando, FL: A. Taussig and Leann Goodwin; The Lindner Center, Cincinnati, OH: D. Kereiakes and Darlene Rock; Jim Moran Heart and Vascular Research Institute, Ft Lauderdale, FL: A. Niederman, Terri Kellerman, and Cynthia Toot; Scripps Green Hospital, La Jolla, CA: R. Schatz and Heather Catchpole; Arizona Heart Institute, Phoenix, AZ: G. Wheatley and Candice Kelly.

Author contributions: Thomas J. Povsic, MD, PhD, and Warren Sherman, MD, had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Povsic and Sherman share joint responsibility for the study concept and design, acquisition of the data, analysis and interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

Study concept and design: Sherman, Povsic, O'Connor, Spencer, and Owens. Acquisition of data: Joseph and Povsic. Analysis and interpretation of data: Povsic, Sherman, and O'Connor. Drafting of the manuscript: Povsic and Sherman. Critical revision of the manuscript for important intellectual content: Henry, O'Connor, and Alexander. Statistical analysis: Roberts and Povsic. Administrative, technical, or material support: Banks, Joseph, Owens, and Spencer. Study supervision: Povsic, Sherman, O'Connor, and Owens.

Disclosures

Funding: The MARVEL-1 trial was supported by Bioheart, Inc.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation 2010;121:e46-215.
2. Losordo DW, Vale PR, Hendel RC, et al. Phase 1/2 placebo-controlled, double-blind, dose-escalating trial of myocardial vascular endothelial growth factor 2 gene transfer by catheter delivery in patients with chronic myocardial ischemia. Circulation 2002;105: 2012-8.
3. Henry TD, Grines CL, Watkins MW, et al. Effects of Ad5FGF-4 in patients with angina: an analysis of pooled data from the AGENT-3 and AGENT-4 trials. J Am Coll Cardiol 2007;50:1038-46.
4. Henry TD, Annex BH, McKendall GR, et al. The VIVA trial: vascular endothelial growth factor in Ischemia for Vascular Angiogenesis. Circulation 2003;107:1359-65.
5. Galinanes M, Loubani M, Davies J, et al. Autotransplantation of unmanipulated bone marrow into scarred myocardium is safe and enhances cardiac function in humans. Cell Transplant 2004;13:7-13.
6. Orlic D, Kajstura J, Chimenti S, et al. Mobilized bone marrow cells repair the infarcted heart, improving function and survival. Proc Natl Acad Sci USA 2001;98:10344-9.
7. Murry CE, Soonpaa MH, Reinecke H, et al. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. Nature 2004;428:664-8.
8. Bearzi C, Rota M, Hosoda T, et al. Human cardiac stem cells. Proc Natl Acad Sci USA 2007;104:14068-73.
9. Beltrami AP, Barlucchi L, Torella D, et al. Adult cardiac stem cells are multipotent and support myocardial regeneration. Cell 2003;114: 763-76.
10. Smith RR, Barile L, Cho HC, et al. Regenerative potential of cardiosphere-derived cells expanded from percutaneous endomyocardial biopsy specimens. Circulation 2007;115:896-908.
11. Ghostine S, Carrion C, Souza LC, et al. Long-term efficacy of myoblast transplantation on regional structure and function after myocardial infarction. Circulation 2002;106:I131-6.
12. Taylor DA, Atkins BZ, Hungspreugs P, et al. Regenerating functional myocardium: improved performance after skeletal myoblast transplantation. Nat Med 1998;4:929-33.
13. Pouzet B, Vilquin JT, Hagège AA, et al. Factors affecting functional outcome after autologous skeletal myoblast transplantation. Ann Thorac Surg 2001;71:844-50.
14. He KL, Yi GH, Sherman W, et al. Autologous skeletal myoblast transplantation improved hemodynamics and left ventricular function in chronic heart failure dogs. J Heart Lung Transplant 2005;24: 1940-9.
15. Menasché P, Hagège AA, Scorsin M, et al. Myoblast transplantation for heart failure. Lancet 2001;357:279-80.

16. Menasché P, Hagège AA, Vilquin JT, et al. Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. J Am Coll Cardiol 2003;41:1078-83.
17. Dib N, McCarthy P, MacLellan R, et al. Two-year follow-up of the feasibility and safety of autologous myuoblast transplantation for ischemic cardiomyopathy in patients undergoing coronary artery bypass grafting (abstract). Circulation 2004;110:III-51.
18. Smits PC, van Geuns RJ, Poldermans D, et al. Catheter-based intramyocardial injection of autologous skeletal myoblasts as a primary treatment of ischemic heart failure: clinical experience with six-month follow-up. J Am Coll Cardiol 2003;42:2063-9.
19. Sherman W, Henry T, Chronos N, et al. Results of the MYOHEART Trial: a phase 1 study of skeletal myoblasts in patients with congestive heart failure. Paper presented at: Transcatheter Cardiovascular Therapeutics (TCT); October, Washington, DC; 2007.
20. Menasche P, Alfieri O, Janssens S, et al. The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. Circulation 2008;117:1189-200.
21. Serruys P. Final results of a phase II-a, randomized, open-label trial to evaluate intramyocardial autologous skeletal myoblast transplantation in congestive heart failure patients: the SEISMIC trial. Paper presented at: the American College of Cardiology 57th Annual Scientific Session; March, Chicago, IL; 2008.
22. Dib N, Dinsmore J, Lababidi Z, et al. One-year follow-up of feasibility and safety of the first U.S., randomized, controlled study using 3-dimensional guided catheter-based delivery of autologous skeletal myoblasts for ischemic cardiomyopathy (CAuSMIC Study). JACC: Cardiovasc Intervent 2009;2:9-16.
23. Mills WR, Mal N, Kiedrowski MJ, et al. Stem cell therapy enhances electrical viability in myocardial infarction. J Mol Cell Cardiol 2007; 42:304-14.
24. Sherman W. MYOHEART US phase I study: 12 month data. Paper presented at: the Fifth Annual Conference on Cell Therapy for Cardiovascular Disease; January, New York, NY; 2008.
25. Siminiak T, Kalawski R, Fiszer D, et al. Autologous skeletal myoblast transplantation for the treatment of postinfarction myocardial injury: phase I clinical study with 12 months of follow-up. Am Heart J 2004; 148:531-7.
26. Piccini JP, Berger JS, O'Connor CM. Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials. Eur Heart J 2009;30:1245-53.
27. Losordo D. Randomized, double-blind, placebo-controlled study of intramyocardial $CD34^+$ cell therapy for refractory angina. Paper presented at: the American College of Cardiology 58th Annual Scientific Session/i2 Summit; March, Orlando, FL; 2009.
28. Losordo DW, Schatz RA, White CJ, et al. Intramyocardial transplantation of autologous CD34+ stem cells for intractable angina: a phase I/IIa double-blind, randomized controlled trial. Circulation 2007;115:3165-72.
29. van Ramshorst J, Bax JJ, Beeres SL, et al. Intramyocardial bone marrow cell injection for chronic myocardial ischemia: a randomized controlled trial. JAMA 2009;301:1997-2004.

Appendix. Individual Patient Data for 6MWT (top panels) and MLWHF Score (bottom panels)