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Intramyocardial Injection of Allogeneic Mesenchymal Precursor Cells in Left Ventricular Assist Device Patients

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Abstract:
BACKGROUND: Intramyocardial administration of allogeneic mesenchymal precursor cells (MPC) injected at the time of left ventricular assist device (LVAD) implantation may contribute to myocardial recovery in advanced heart failure (AHF) patients. This trial, conducted by the NIH-sponsored Cardiothoracic Surgical Trials Network (CTSN) and the Cardiovascular Cell Therapy Research Network (CCTRN), assesses the safety and explores the efficacy of intramyocardial allogeneic MPCs (Mesoblast) as an adjunct to LVAD.
METHODS: Thirty patients were randomized at 11 sites in this double-blind, sham procedure controlled trial evaluating a single intramyocardial injection of MPCs on safety, functional status, myocardial function, cardiomyocyte regeneration, and neovascularization in patients with AHF, implanted with an LVAD as bridge to cardiac transplantation (BTT) or destination therapy (DT). Patients were randomly assigned (2:1) to 25 million MPCs or medium alone. The primary safety endpoint is the incidence of infectious myocarditis, myocardial rupture, neoplasm, hypersensitivity reaction, and immune sensitization (90 days post randomization). The key efficacy endpoint is functional status and ventricular function, while weaned from LVAD support (90 days post randomization); other secondary endpoints include neurocognition, adverse events, anti-HLA antibody sensitization, cardiomyocyte regeneration, phenotypic and functional analyses, and chemo- and cytokine quantification. All patients are followed until transplant or until 12 months post randomization, whichever comes first.
RESULTS: Enrollment was completed in 15 weeks. All patients have met the primary 90 day efficacy endpoint, and investigators remain blinded to all outcomes until the last patient completes 1 yr final assessment in 08/13.
CONCLUSION: This trial will provide important information with regard to the safety and efficacy of MPC injection at the time of LVAD implantation.

Table. Baseline Characteristics

	MPCs (N=20)	Control (N=10)
Age	55.1 (±15.4)	62.2 (±7.8)
Male	17 (85%)	8 (80%)
LVEF (%)	17.3 (±3.9)	18.2 (±4.6)
Ischemic Cardiomyopathy	7 (35%)	4 (40%)
LVAD Indication		
BTT	7 (35%)	2 (20%)
DT	13 (65%)	8 (80%)

Clinical Trial:
Hypothesis and Purpose: The primary objective of this exploratory trial is to provide evidence of the safety of direct myocardial injection of a single dose of MPCs in LVAD recipients.
The secondary objective is to explore the efficacy of injecting MPCs into the native myocardium of LVAD recipients.
Intramyocardial injection of mesenchymal precursor cells (MPC) in patients with advanced heart failure who are treated with left ventricular assist device (LVAD) implantation may result in a renewable source of proliferating functional cardiomyocytes, as well as induce development of capillaries and larger size blood vessels to supply oxygen and nutrients to endogenous myocardium and newly-implanted cardiomyocytes, and release factors capable of paracrine signaling.
Study Design and Methods: This is a prospective, multi-center, double-blind, randomized, single dose cohort, sham procedure controlled trial to define the safety and feasibility, and to explore the efficacy of intra-myocardial injection of mesenchymal precursor cells (RevascorTM) on functional status, myocardial function, cardiomyocyte regeneration, and neovascularization in patients with advanced heart failure, implanted with an FDA-approved LVAD as either a bridge to cardiac transplantation or for destination therapy. All patients will be followed until cardiac transplantation (for BTT patients) or until 12 months post randomization, whichever comes first.
Sample Size: 30 patients
Population Studied: Patients with end-stage heart failure, either ischemic or non-ischemic etiology, who are being evaluated for LVAD implantation as a bridge-to-transplant (BTT) or destination therapy (DT)
Intervention(s): Patients will be enrolled in a single dose cohort randomized in a 2:1 allocation to intramyocardial injection of study product or control (cryoprotective media alone) at the time of LVAD implantation:
o Group 1 (n=20): 25 million MPC (Revascor™)

o Group 2 (n=10): 50% Alpha-MEM/42.5% ProFreeze NAO Freezing Medium/7.5% DMSO (control)
Power Calculations:
This sample size is based on a Bayesian approach computing the posterior distribution that active therapy is superior to control. A total sample size of 30 patients allows detecting an approximate tripling of the odds that active therapy is superior from an assumed prior belief of equal benefit (i.e., from 50% probability of active therapy's superiority, or 1:1 odds, to 75% or 3:1 odds) with probability 75% or more if the absolute probability of a successful outcome (ability to tolerate weaning) with active therapy is about 10-15% higher than for control.
Primary End Points: The primary safety endpoint is the incidence of the following potential study-intervention related adverse events at 90 days post randomization:
o Infectious myocarditis
o Myocardial rupture
o Neoplasm
o Hypersensitivity reaction
o Immune sensitization
Secondary End Points: The key efficacy endpoint is functional status and ventricular function, while weaned from LVAD support, at 90 days post randomization.
Secondary endpoints include:
o Echocardiographic assessments of the myocardial size and function by transthoracic echocardiography with LVAD at full support, and as tolerated at 1and 5 minutes (limited echo) and 15 minutes following initiation of wean, including:
o Left ventricular end-diastolic and end-systolic dimensions;
o Left ventricular fractional shortening;
o Regional wall motion score index (WMSI) at limited time points only;
o RV function (Qualitative: normal, mild, moderate, severe);
o RVSP from tricuspid regurgitation (TR) jet;
o Global and regional strain from speckle tracking
o 6 Minute walk as tolerated at 20 (± 10) minutes following initiation of wean
o Ability to tolerate wean from LVAD support for 30 minutes without signs and symptoms of hypoperfusion (Note: 90 day time point is the key efficacy endpoint)
o Duration of ability to tolerate wean from LVAD support, without signs and symptoms of hypoperfusion
o Neurocognition at 90 days post randomization
o Incidence of study intervention-related adverse events
o Incidence of all serious adverse events
o Anti-HLA antibody sensitization while on LVAD support
o Cardiomyocyte regeneration at explant
o Cell Engraftment and Fate at explant
o Survival to cardiac transplantation
Outcome(s) Statistical Plan or Main Results:
The last protocol defined data collection for this study is anticipated in August 2013 and then data analysis will commence.
Analytical Plan:
Non-informative beta(1,1) probability densities are used to represent each treatment's prior probability of success. Thus, prior to any data collection the probability that active therapy is superior to control is 50%; a state that reflects equipoise. Given the observed data, the prior distribution will be updated using a binomial likelihood to compute the posterior probability that active therapy is superior to control. An increase in the posterior probability that active therapy is superior to control to a level providing reasonable assurance of an efficacy signal (e.g., 75%), without safety concerns, would warrant additional study of MPC therapy.
Author Disclosure Information: D.D. Ascheim: Consultant/Advisory Board; Modest; BackBeat Medical, Inc, Velomedix. Y. Naka: Consultant/Advisory Board; Modest; Thoratec Co., Transmedics Inc., Medtronics. N.G. Smidera: None. L.A. Moye: None. S. Lee: None. C.T. Klodell: None. A. Szady: None. M.K. Parides: None. N. Jeffries: None. D. Skerret: Employment; Significant; Mesoblast Ltd. Ownership Interest; Significant; Mesoblast Ltd. D.A. Taylor: Ownership Interest; Significant; Miromatrix Medical Inc. K. Margulies: None. C. Milano: None. J.G. Rogers: Consultant/Advisory Board; Significant; Thoratec. T. Dewey: None. E. Eichorn: None. B. Sun: None. D. Feldman: None. D. Goldstein: Honoraria; Modest; Heartware Inc. Consultant/Advisory Board; Modest; Thoratec Inc,, Terumo Inc. P.T. O'Gara: None. R.D. Simari: None. S. Skarlatos: None. W. Taddei-Peters: None. M. Miller: None. E. Bagiella: None. A.C. Gelijns: None. J.Y. Woo: None.

Application Information (Complete):
*Is this a Late Breaking Clinical Trial (1st presentation of completed trial), a Clinical Trial Update or High Impact Information from Clinical Registries?
: Late Breaking Clinical Trial
*Is this a study testing a treatment/intervention to improve health outcomes?: Yes
*Is this a First in Man therapeutic trial?: Yes
*Multi-Center study?: Yes
*Number of Sites: : 11
*Final Enrollment Month: August
*Final Enrollment Year: 2012
*Final Data Availability (Month): August
*Final Data Availability (Year): 2013
*Results being presented elsewhere?: No
1. Company Name
: Mesoblast, Ltd.
Associated Drugs or Products
: allogeneic mesenchymal precursor cells (MPC)
Contact Name : Donna Skerret
Phone/Email : 212-880-2060/ donna.skerrett@mesoblast.com
*Disclosure: There are unlabeled/unapproved uses of drugs or products.
Product One: : allogeneic mesenchymal precursor cells (MPC)
*Description : This trial assesses the safety and explores the efficacy of intramyocardial allogeneic MPCs as an adjunct to LVAD.

Principal Investigator (Complete):

First Name: : Deborah D.
Last Name: : Ascheim, MD

Payment (Complete): Your credit card order has been processed on Monday 24 June 2013 at 4:53 PM.
Additional Info (Complete):
*: Yes
If there is an ACRONYM for your trial/study, please type it in the space provided. If no, please enter No in the space provided. : No
Has this research received full or partial funding from the American Heart Association?: No

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