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Randomized, double-blind, phase I/II study of intravenous allogeneic mesenchymal stromal cells in acute myocardial infarction

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Abstract

Background aims. Cell therapy is promising as an exploratory cardiovascular therapy. We have recently developed an investigational new drug named Stempeucel (bone marrow–derived allogeneic mesenchymal stromal cells) for patients with acute myocardial infarction (AMI) with ST-segment elevation. A phase I/II randomized, double-blind, single-dose study was conducted to assess the safety and efficacy of intravenous administration of Stempeucel versus placebo (multiple electrolytes injection). *Methods.* Twenty patients who had undergone percutaneous coronary intervention for AMI were randomly assigned (1:1) to receive intravenous Stempeucel or placebo and were followed for 2 years. *Results.* The number of treatment-emergent adverse events observed were 18 and 21 in the Stempeucel and placebo groups, respectively. None of the adverse events were related to Stempeucel according to the investigators and independent data safety monitoring board. There was no serious adverse event in the Stempeucel group and there were three serious adverse events in the placebo group, of which one had a fatal outcome. Ejection fraction determined by use of echocardiography showed improvement in both Stempeucel (43.06% to 47.80%) and placebo (43.44% to 45.33%) groups at 6 months ($P = 0.26$). Perfusion scores measured by use of single-photon emission tomography and infarct volume measured by use of magnetic resonance imaging showed no significant differences between the two groups at 6 months. *Conclusions.* This study showed that Stempeucel was safe and well tolerated when administered intravenously in AMI patients 2 days after percutaneous coronary intervention. The optimal dose and route of administration needs further evaluation in larger clinical trials (http://clinicaltrials.gov/show/NCT00883727).

Key Words: *acute myocardial infarction, bone marrow, cell therapy, mesenchymal stromal cells*

Introduction

Myocardial infarction is the single largest cause of death worldwide. The Global Burden of Diseases study reported that the incidence of death caused by coronary heart disease will double in developing countries by 2020 [1]. Despite significant advances in treatment, ventricular dysfunction remains the major cause of morbidity and mortality in these patients. Cellular therapy for myocardial infarction (MI) is gaining importance. Intracoronary infusion of different cell populations (circulating progenitor cells, bone marrow–derived progenitor cells, bone marrow cells, peripheral blood stem cells, hematopoietic stem cells and allogeneic bone marrow mesenchymal stromal cells) have been used in acute MI (AMI) and in some instances with promising results [2–6]. There are several publications discussing the role of stem cell therapy in ischemic heart disease [7–10].

Stempeucel is *ex vivo*–cultured allogeneic bone marrow–derived mesenchymal stromal cells (BMMSC) that have both myogenic and angiogenic potential and is being explored for its therapeutic potential for regeneration/repairing injured myocardial tissue. Furthermore, these cells are nonimmunogeneic [11–13] and have anti-inflammatory properties and facilitate vasculogenesis by increasing vascular endothelial growth factor (VEGF) level [14,15].

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Table I. Eligibility criteria.

Inclusion criteria	Exclusion criteria
Patients with STEMI ages between 20 and 70 years, either men or women with non–child-bearing potential, after 2 days of successful PCI.	History of acute/chronic inflammatory condition or severe aortic stenosis or insufficiency; severe mitral stenosis or severe mitral insufficiency.
Patient has global left ventricular systolic dysfunction with an ejection fraction of <50% and >30%.	Severe co-morbidity associated with a reduction in life expectancy of <1 year.
Electrocardiogram with sign of acute anterior MI with ST-elevation ≥2 mm in at least two of the following: leads I, AVL or V_1-V_6 or electrocardiogram with sign of acute inferoposterior MI with ST-elevation ≥1 mm on all of the following leads: II, III and V_5-V_6 or ST-elevation ≥2 mm in at least two of the leads.	Advanced renal dysfunction and creatinine ≥2 mg%.
Target lesion is located in the proximal section of the left anterior descending, left circumflex or right coronary artery.	Advanced hepatic dysfunction.
Patient with AMI within 10 days before intraperitoneal administration.	Clinically serious and/or unstable intercurrent infection, medical illnesses or conditions that are uncontrolled or whose control, in the opinion of the investigator, may be jeopardized by participation in this study or by the complications of this therapy.
Normal liver and renal function.	Previous MI.
Able to understand study information provided.	Patients already enrolled in another investigational drug trial.
Able to give voluntary written consent.	History of severe alcohol or drug abuse within 3 months of screening.
	Women with child-bearing potential or who are pregnant or lactating.
	Positive test for human immunodeficiency virus 1, hepatitis C virus, hepatitis B virus, syphilis and cytomegalovirus (immunoglobulin M).
	Patients contraindicated for MRI.

BMMSCs have been shown to home, accumulate and in some cases differentiate around the diseased micro-environment [16,17]. The increased vascular permeability and expression of adhesion molecules such as integrin assist in MSC homing [18–20]. The migratory capacity of these cells is dependent on natural growth factors such as VEGF, stromal cell–derived factor-1 (SDF1) and stem cell factor. The expression of VEGF, SDF1 and stem cell factor is highly unregulated in the hypoxic damaged tissue such as cardiac tissue and is responsible for the recruitment of the stem cells to assist in the repair mechanism and subsequent improvement in cardiac function [21–23]. On the basis of the homing properties of these cells, this study was designed to deliver the cells by intravenous route and to evaluate the safety and possible efficacy of Stempeucel in patients with AMI.

Methods

Study design and criteria for enrollment

This study was a phase I/II randomized, double-blind, placebo-controlled, multicentric trial to evaluate the safety and efficacy of Stempeucel administered to patients with ST-elevated myocardial infarction (STEMI) 2 days after percutaneous coronary intervention (PCI). The study conformed to the *Declaration of Helsinki* and followed International Conference on Harmonisation–Good Clinical Practice guidelines and was conducted in accordance with the Guidelines for Stem Cell Research and Therapy developed by the Department of Biotechnology and Indian Council of Medical Research jointly in 2007. The protocol was approved by the Drug Controller General of India (Indian Food and Drug Administration) and by the Institutional Ethical Committees of the four participating hospitals in India. The study was registered in the National Institutes of Health website (http://clinicaltrials.gov/show/NCT00883727) and was conducted from July 2009 to November 2011. Thirty patients were screened (as per criteria in Table I) after written informed consent was obtained. Computer-generated block randomization was performed centrally to randomly assign 20 patients to Stempeucel or to the placebo group in a 1:1 ratio (Figure 1). An independent data safety monitoring board (DSMB), which consisted of safety physicians and biostatisticians, was established to assess the progress of this study.

Preparation and composition of Stempeucel and placebo

The investigational medicinal product (IMP) Stempeucel was constituted by allogeneic BMMSC obtained from bone marrow aspirates from consenting donors who were not human leukocyte antigen (HLA)-matched to the recipients. Healthy bone marrow donors were tested according to 21 Code of Federal Regulations 640, Food and Drug Administration donor suitability and Indian Council of Medical Research guidance for healthy bone marrow donor screening. BMMSCs were obtained from bone marrow samples of healthy donors between the ages of 20 and 35 years after informed consent was obtained. The protocol was approved by the institutional ethics committee. Briefly, 60 mL of bone marrow aspirate was diluted (1:1) with knockout Dulbecco's modified Eagle's medium (KO-DMEM; Gibco-Invitrogen, Grand island, New York, USA), and centrifuged at