Circulating Blood Derived Progenitor Cell Therapy In Acute Myocardial Infarction: A Randomized Controlled Trial

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A. Study Purpose and Rationale

Early mortality from acute myocardial infarction has been significantly reduced by the timely restoration of blood flow in the occluded artery. However, post infarction morbidity due to replacement of damaged myocardium by non-contractile scar tissue remains a significant problem. Recent insight into post-infarction remodeling suggests that damaged myocytes hypertrophy rather than replicate, and that the hypertrophied cells have impaired contractility and are prone to apoptosis as a result of an inadequate neovascular response. The resultant necrotic tissue is unable to be reconstituted by existing terminally differentiated myocytes and is replaced by a fibrous scar. In recent studies, stem cells derived from either bone marrow[1] or peripheral blood [1-2] were shown to be capable of differentiating into cardiac myocytes and/or neovascular structures. Animal models have demonstrated that autologous stem cells transplanted after transient coronary artery ligation are capable of restoring functional myocardium[3]. In a study of the feasibility and safety of autologous stem cell transplantation in human subjects with acute myocardial infarction, 20 patients were studied and demonstrated an improvement in several measures of left ventricular function as compared to unmatched controls[1]. There were no untoward proinflammatory or arrhythmia related events in the patients who received the stem cells. A more definitive study of the therapeutic potential of stem cell technology following acute MI is needed.

B. Study Design and Statistical Analysis

The hypothesis that autologous stem cell transplantation immediately following an acute myocardial infarction leads to improved ventricular function will be tested in a randomized controlled trial. Following cardiac catheterization and reperfusion, patients will be randomized, by conventional randomization methods, to receive autologous stem cell transplants or placebo. There will be no crossover between groups. Assessment of left ventricular function by means of global ejection fraction will be determined by transthoracic echocardiography immediately following MI and at 4 months. Based on an assumed treatment-related improvement in ejection fraction of 8.5 percent with a standard deviation of 10.86, 45 subjects will be recruited in each arm for a two-sided significance level of 5 percent and 80 percent power. Change in ejection fraction over time will be presented as mean +/- SD. Statistical comparisons will be made by unpaired T-Test for data distributed normally. Statistical significance will be assumed at a value of $p<0.05$

C. Study Procedure

All subjects will undergo coronary catheterization with stenting of the occluded artery prior to randomization. Patients will then be randomized to receive an infusion of circulating blood-derived progenitor cells (CPCs) or a placebo infusion. Two hundred fifty mL of arterial blood will be collected from all patients prior to sheath removal during catheterization. CPCs will be prepared ex-vivo according to a previously published protocol[8, 9] and reinfused into the peripheral circulation of test subjects on post-MI day 4. No additional pain, discomfort or inconvenience related to the treatment is anticipated. Two-dimensional transthoracic echocardiography will be performed during the initial hospitalization and at 4 months post-MI. Measurement of end-systolic and end-diastolic volume will be made by a single blinded cardiologist trained in echocardiography and used to calculate the ejection fraction by standard formula ([EDV-ESV]/EDV x100). Clinical and laboratory data will be collected prospectively during follow-up

visits at 2 weeks, 2 months and 4 months time. Based on an estimated incidence of 50 ST-elevation MI annually at CPMC, enrollment of subjects will be completed in 24-months with completion of the study in 30-36months.

D. Study Drugs

Autologous stem cells derived from peripheral blood and expanded ex vivo in a sterile, infection-free manner will be given to study subjects. Control subjects will receive a placebo infusion of normal saline. Given the investigational nature of the study drug, an interim analysis will be performed at 12-months with specific focus on side effect profiles and adverse event rates in the two groups. Specifically data on incidence of stent occlusion requiring repeat intervention, recurrent myocardial ischemia, peripheral thrombosis, bleeding, malignant arrhythmia, mechanical complications and death will be compared.

E. Medical Devices

N/A

F. Study Questionnaires

N/A

G. Study Subjects

Consecutive patients between the age of 18 and 80 presenting to the Emergency Department or referred from outside institutions with a first acute ST-elevation myocardial infarction will be eligible for inclusion. Patients will be excluded if they have cardiogenic shock (defined as systolic blood pressure <80 mm Hg requiring intravenous pressors or IABP), major bleeding requiring blood transfusion after acute reperfusion, a history of leukopenia, thrombocytopenia, hepatic or renal dysfunction, known malignancy or other bone marrow disease.

H. Recruitment of Subjects

Consecutive patients will be approached for participation in the study and recruited according to the policy of the study institution.

I. Confidentiality of Study Data

All clinical information will handled in a confidential manner in accordance with the confidentiality policy of the study institution. Data will be coded and stored in a secure location accessible only to the study investigators.

J. Potential Conflict of Interest

There are no potential conflicts of interest for this study.

K. Location of the Study

The study will be conducted at Columbia Presbyterian Medical Center.

L. Potential Risks

Because of the experimental nature of the study drug, a detailed side effect profile is unknown. Preliminary studies did not demonstrate a significant adverse reaction profile for the drug. There is a theoretic risk of arrhythmia related to formation of new electrical networks from stem cell derived myocytes. There is a risk of infection related to the ex vivo expansion of stem cells.

M. Potential Benefits

Decreased long-term morbidity from ischemia related congestive heart failure is hypothesized to occur in the treatment group. Subjects may or may not benefit from participation in the study

N. Alternative Therapies

N/A

O. Compensation to Subjects

Subjects will not receive monetary compensation for participation in the study.

P. Cost to Subjects

Subjects will not incur any additional costs as a result of participation in the study.

Q. Minors as Research Subjects

N/A

R. Radiation or Radioactive substances

N/A

S. References

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