ADULT STEM CELL TRIAL AT BARTS and THE LONDON NHS TRUST

(REGENERATE – IHD & REGENERATE – DCM)

• REGENERATE - IHD
  Randomised Control Trial To Compare The Effects Of G-CSF And Autologous Bone Marrow Progenitor Cells Infusion On Quality Of Life And Left Ventricular Function In Patients With Heart Failure Secondary to Ischaemic Heart Disease

• REGENERATE – DCM
  Randomised Controlled Trial To Compare The Effects Of G-CSF And Autologous Bone Marrow Progenitor Cells On Quality Of Life And Left Ventricular Function In Patients With Idiopathic Dilated Cardiomyopathy

BACKGROUND

Pluripotent Primitive Cells, Cardiac Repair and Regeneration

The heart is an organ of limited regenerative capacity and as such has insufficient potential to repair itself. The response to injury comprises adaptive mechanisms such as the opening up of collateral vessels, the hypertrophy of pre-existing cardiomyocytes and the scar formation by stimulation of fibroblasts (remodelling). Recent work that has analysed atrial tissue from sex mismatched heart transplant recipients has demonstrated that primitive cells can migrate into the transplanted heart from the recipient in small numbers. Histological examination has shown that these cells express surface markers demonstrating differentiation into various cell types (cardiomyocytes, endothelial cells and vascular smooth muscle cells) had taken place. This important observation implies that there may be a background level of cellular renewal by engraftment and differentiation of primitive cells that is insufficient to deal with significant levels of myocyte damage. The most likely source of these primitive cells is the bone marrow. Experiments in mice have demonstrated homing and engraftment of labelled bone marrow derived progenitor cells to the site of myocardial infarction. As before, histological examination demonstrated that these labelled cells had undergone a process of differentiation and expressed cardiomyocyte surface markers.

Since it had previously been shown that direct injection of bone marrow progenitor cells into the perinfarct zone in a mouse model of myocardial infarction lead to a repopulation of myocytes and improvement in left ventricular function the concept that the bone marrow may provide a source of primitive cells capable of repairing the damaged heart evolved. Orlic and co-workers were able to demonstrate that primitive cells could be mobilised from the bone marrow in a mouse model of myocardial infarction using a combination of the cytokines stem cell factor (SCF) and granulocyte colony stimulating factor (G-CSF). Treatment with these cytokines for 5 days prior to coronary artery ligation and for 3 days afterwards resulted in reduction in mortality, infarct size, magnitude of cavity dilatation and diastolic stress at 27 days post-infarct compared with saline-injected animals. Left ventricular ejection fraction, as measured by echocardiography, was greater in cytokine-treated animals compared with controls.
Stem Cell Therapy to Treat Cardiovascular Disease in Man

Several groups have published preliminary data demonstrating the safety and efficacy of stem cell administration to treat cardiovascular disorders in man. Autologous bone marrow derived progenitor cells have been administered to patients undergoing acute myocardial infarction by direct intracoronary and intracardiac injection \(^4^6\). Although the published data is for short periods of follow-up, all studies report some improvement in indices of cardiac function or symptoms and no immediate adverse events. Patients with heart failure secondary to ischaemic heart disease have also been shown to derive benefits in cardiac performance and symptoms when treated with autologous bone marrow derived progenitor cells \(^7^9\).

To date, one study has reported on the use of G-CSF to treat patients with heart failure secondary to ischaemic heart disease \(^10\). At this moment in time the study is recruiting but reports no adverse events in the group of patients treated with G-CSF. Animal work however suggests that although G-CSF can mobilise bone marrow derived progenitor cells, these cells may require a separate stimulus to home and engraft at the site of myocardial damage \(^11\). Work by Professor Zeiher’s group in Frankfurt, who have now administered intracoronary bone marrow derived progenitor cells to approximately 200 patients with ischaemic heart disease, suggest that a period of myocardial ischaemia is required for homing and engraftment of the stem cells to occur (personal communication Prof A Zeiher, University of Frankfurt). The ischaemia induced by balloon inflation in the proximal coronary artery at the time of stem cell infusion (necessary to prevent spillage into the peripheral circulation) would appear to be sufficient for homing and engraftment without leading to a rise in cardiac enzymes that would suggest myocardial damage.

To date, two direct methods of introducing stem cells to the myocardium have been used in man: direct intracoronary injection \(^5\) and direct intramyocardial injection \(^12\). Whilst intracoronary injection has the advantage of being less invasive than direct intramyocardial injection, it has the disadvantage that patients with coronary artery occlusion are thus unable to receive stem cells directly to the site of injury unless the occluded artery supplying that region can be reopened. Such procedures to open chronically occluded coronary arteries are technically complicated and associated with a low long-term patency. Direct intramyocardial injection has recently been shown to be feasible using a percutaneous technique and non-fluoroscopic mapping system (NOGA) \(^12\). Therefore, given the high proportion of patient that will have coronary artery occlusion as a result of their ischaemic heart disease, the technique of direct intramyocardial stem cell delivery has been included as an arm of the interventional part of this study.

The aim of this project is to investigate whether G-CSF, alone or in combination with direct intracoronary autologous bone marrow derived progenitor cell injection, is capable of improving symptoms and cardiac function in patients with heart failure secondary to ischaemic heart disease. The design of the study seeks to determine whether a significant improvement in cardiac function and symptoms can be achieved by the relatively non-invasive procedure of G-CSF administration or whether an invasive approach requiring direct intracoronary injection provides the optimal improvement. Only symptomatic patients with no further treatment options will be considered for this study.

There is a unique opportunity to refer symptomatic heart failure patients caused by Idiopathic dilated cardiomyopathy (DCM) or Ischaemic heart disease (IHD) who have no further treatment options, to participate in these clinical trials. If you think you have any patients who may be suitable for such studies please contact the Cardiac Research team at The London Chest Hospital.
Patients will be randomised to either non-intervention or intervention.

Follow-up at 6 months and 1 year

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References


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