Stem Cell Therapy in Acute Myocardial Infarction
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Abstract

Over the last several years, much headway has been made in the arena of coronary artery disease, specifically in the rapid diagnosis and revascularization therapy of acute myocardial infarction. Despite these advances however, given the natural history of acute myocardial infarction (AMI), a significant proportion of patients are left with significant morbidities by consequences of impaired left ventricular function. Stem cell therapy, which was initially introduced as a novel approach to regenerate injured cardiac myocytes, has widely been gaining popularity as a feasible strategy for repairing injured myocardial muscle tissue.

Over a decade of basic and clinical research has gone into determining the effectiveness of targeted progenitor stem cell delivery in the improvement of myocardial function and cardiac physiology. Our paper is a general review of the stem cells therapy in patients who have had acute myocardial infarction. Although, much of the data thus far has been suggestive of the potential benefit of this approach in human models, a quest for a definitive answer is still underway. In the treatment of acute myocardial infarction, targeted stem cell therapy, at the very least, is a union of cellular biology and clinical cardiology, which albeit nascent in its development, has laid the framework for a clear direction into the future of cardiovascular medicine.

Introduction

“Ideal cardiovascular health” is defined by the absence of clinically manifest cardiovascular disease and the simultaneous presence of optimal levels of all 7 health behaviors (lean body mass, avoidance of smoking, participation in physical activity, and healthy dietary intake) and health factors (untreated total cholesterol <200 mg/dL, untreated blood pressure <120/80 mm Hg, and fasting blood glucose <100 mg/dL) [1].

On the basis of unpublished data from the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS) of National Heart, Lung, and Blood Institute (NHLBI), this year 785000 Americans will have a new coronary attack and 470000 will have a recurrent attack. The estimated annual incidence of MI is 610000 new attacks and 325000 recurrent attacks [1]. The American Heart Association (AHA) recently created a new set of ‘Impact Goals’ for the current decade. The aim, by 2020, is to improve the cardiovascular health of all Americans by 20%, while reducing deaths from cardiovascular disease and stroke by 20% [2].

The early biochemical consequence of myocardial ischemia is the cessation of aerobic metabolism within seconds, leading to inadequate production of high-energy phosphates and accumulation of potentially noxious metabolites [3]. Because of the exquisite dependence of myocardial function on oxygen, severe ischemia induces loss of contractility within 60 seconds. Nevertheless, these early changes are potentially reversible. As demonstrated both experimentally and in clinical studies, only severe ischemia lasting 20 to 30 minutes or longer leads to irreversible necrosis of cardiac myocytes [3].

The current standards of practice for treatment of AMI are percutaneous coronary intervention (PCI), thrombolytic therapy if PCI facility is not available when appropriate [4]. The aim of any medical or surgical therapy however, is to establish prompt revascularization and limit the degree of myocardial injury. Yet the success of any of these therapies is dependent on one key factor, the time to presentation. Given this lacuna in the treatment of AMI, the need to investigate for therapies that add incremental benefit to the current established treatment options is an ongoing endeavor. It was promising to note that the early effects achieved with bone marrow cell (BMC) therapy is comparable to what is achieved by established therapies including acute PCI, angiotensin-converting-enzyme inhibition, or β-blocker therapy [5].

Given the uncertainty of myocardial salvage, dictated by the degree of necrosis from the sentinel event, it soon became clear that in order to change the long term outcomes of AMI, we needed to search for a therapy that takes the time to presentation out of the equation. A possible solution to that dilemma appeared in the form of targeted stem cell therapy.

Evidence of resident cardiac stem cells (SC) began to formulate in studies of human patients who had died within 4-12 days after MI [6]. This concept further gained strength looking at patients who had undergone gender-mismatched heart transplants, in which hearts from female donor were implanted into male recipients, and at the time of death (ranging from 4 to 552 days after transplant), all donor hearts displayed Y-chromosome-positivity, suggesting that SC came from some location outside the heart [6].

Efficacy data suggests its potential to improve left ventricular (LV) function recovery beyond current state of the art therapy, but results are mixed, modest at best and do not supports true cardiomyogenesis. Hence, due to its complexity, costs and remaining uncertainties, it is still too early to implement progenitor cell therapy in its current form as a standard treatment strategy for ischemic heart disease [7].

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Received September 27, 2012; Accepted November 02, 2012, Published November 05, 2012


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Types of Stem Cells

Several different populations of cells have been studied for their use in post MI patients. The most common types are enlisted in table 1.

Most clinical studies have used unfractionated bone marrow cells as the delivery product, postulating that stem and progenitor cells within this population are the biologically relevant therapeutic agents [8].

However, it is the embryonic stem cells and induced pluripotent stem cells which are the only cell types that currently have the potential to generate bona fide cardiomyocytes on a scale that may potentially replace the cell numbers lost in AMI [7].

Stem cells may be classified as autologous or allogenic, depending on their origin. Allogenic cells provide a promising option for stem cell therapy, given that they are free from the immunogenic complications and also the risks of malignancy. However, autologous cells have fairly limited differentiation potential, when compared with allogenic stem cells. SC may also be subdivided into adult cells and fetal and embryonic cells depending on the source they were derived from.

Embryonic stem cells

Embryonic stem cells (ESC) are derived from the blastocyst (inner cell mass) of human embryos prior to implantation. They have the capability to differentiate into any cell from the three germ lines, one of which is cardiac myocytes. However, their inherent totipotency also predispose to tumor formation including teratomas, which have been observed in animal models [9]. Additionally, there is controversy surrounding the ethical issues of ESC use [10].

Human umbilical cord cells

Cord blood contains a large number of non-hematopoietic stem cells which rarely express human leukocyte antigen (HLA) class II antigens and appear to be immunologically naive, thus reducing the risk of rejection. In animal models of AMI injection of human umbilical cord blood cells (hUCBC) is associated with significant reductions in infarct size, particularly when given by the intramyocardial route [11].

Fetal cardiomyocytes

These are multipotent cells which already have a similar phenotype to cardiac cells. However, there is use is fraught with similar concerns about ethical appropriateness, as is with ESC. Furthermore, these cells have immunogenicity, necessitating the use of immune suppression post transplant.

<table>
<thead>
<tr>
<th>TYPES OF STEM CELLS</th>
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<tr>
<td>Embryonic Stem Cells</td>
</tr>
<tr>
<td>Human Umbilical Cord Cells</td>
</tr>
<tr>
<td>Fetal Cardiomyocytes</td>
</tr>
<tr>
<td>Induced Pluripotent Stem Cells</td>
</tr>
<tr>
<td>Resident Cardiac Stem Cells</td>
</tr>
<tr>
<td>Adipose and Skeletal Muscle Derived Stem Cells</td>
</tr>
<tr>
<td>Bone Marrow Derived Stem Cells</td>
</tr>
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</table>

Table 1: Types of Stem Cells.
Progenitor cells can be delivered either via the transvascular approach, peripherally or via retrograde administration through the coronary sinus or by direct intramyocardial injection [7].

**Intracoronary infusion**

This technique is reminiscent of that used in coronary angioplasty. Stem cells are infused under pressure via a balloon catheter while simultaneously occluding antegrade coronary blood flow. A preclinical study in dogs raised concerns regarding the possibility of microinfarcts caused by intracoronary injection of mesenchymal stromal cells [20] and there is likely to be a safety threshold with regards to the size and dose of cells delivered using the intracoronary route. The advantage of intracoronary delivery is that cells are directly injected into areas of good blood supply, rich in nutrients and oxygen, which is essential for cell survival. Myocardial ischemia is a major stimulus for incorporation of circulating progenitor cells, and potently up-regulates the chemotactic factors for neoangiogenesis [21].

**Intravenous (peripheral) infusion**

This technique is applicable only in patients with AMI as it is reliant on physiological homing signals, which are not present in chronic heart failure. Another significant limitation is that only a few cells appear to reach the affected area due to trapping of the cells in the microvasculature of the lungs, liver and lymphoid tissues [22].

Granulocyte colony stimulating factor (G-CSF) is one of the options that have been studied as a method to stimulate and mobilize bone marrow stem cells, but the data published so far has been equivocal on any clear cut benefit of G-CSF.

**Intramyocardial injection**

Quite the opposite of peripheral infusion, intramyocardial injection of stem cells is a technique that is more effective in chronic ischemic cardiomyopathy. In contrast to the AMI setting, these patients are unlikely to release signals from chronically infarcted myocardium to induce stem cell homing and therefore it may be more effective to use intramyocardial injection to deliver the cells to the target area [14]. Stem cells delivered by this method use either a transepicardial or transendocardial approach of injection.

**Transplantation of engineered tissue**

The post-infarct myocardium has drastic changes in tissue microenvironment from the original hypoxic insult, reperfusion injury, and the inflammatory process. Injection of stem cell directly to the dynamic cardiac tissue usually results in significant cell loss either via mechanical damage from the injection or lack of survivability in the harsh post-infarct environment [23,24]. Tissue engineering explores the concept of delivering stem cells on a protected structure to the post-infarct myocardium [25,26]. It has potential for allowing efficient delivery of adequate stem cells by ensuring the transplant stem cell stay on the engineered structure. Additionally, cell signaling factors on the structures can provide a pro-survival microenvironment and pro-differentiation environment for the stem cell. To date, several methods of engineered tissue transplantation has been explored, including collagen patch or extracellular matrix patch, biological sutures, and fibrin micro threads [27-31]. The experimental results generally favors delivering stem cell via engineered tissue versus direct injection in quantity of retaining transplanted stem cells and precision of delivery into the post-infarct-mycordium. Future studies are needed to evaluate the cardiac functional end-point, differentiability of transplanted engineered tissue, and long term survival of the transplanted tissue.

**Mechanism of Action**

In order to produce a therapeutic response, stem cells need to home to the injured myocardium, adhere to and transmigrate through the endothelium, invade the interstitium and finally engraft the damaged myocardium [7]. In addition to the characteristics of the stem cells themselves, the property of the infarcting myocardial tissue, as it passes from a peri-ischemic phase, right until remodeling occurs, plays a tremendous role in the stem cell biophysiology.

MI results in loss of functional myocardium due to hypoxic necrosis, inflammatory change and cardiomyocyte apoptosis. Besides progressing through different stages of inflammation and healing, the dynamic microenvironment in the infarcted tissue also express cardiac cytokines that promotes stem cell migration and homing [32]. Transplanting stem cells to the post-infarct myocardium augment the cytokine effect to attract endogenous stem cells.

Other paracines secreted by stem cells thought to have therapeutic effect by promoting angiogenesis, proliferation of endogenous vascular cells, loosening of fibrotic extracellular matrix, inhibition of cardiomyocyte apoptosis, and regulation of inflammatory response. Together the paracine signals from stem cells expedite wound healing and promote the endogenous myocardial regeneration process [33].

In addition to the paracrine signaling effects, stem cells carry the potential to differentiate into functional myocardium [34]. The supplementation of exogenous stem cell post-MI can engraft into the existing myocardium as functional cardiomyocyte that beats in synchrony with the existing myocardium. Stem cells can also differentiate into smooth muscle cells and vascular endothelial cells. Together, the delivery and differentiation of stem cells replenishes the lost cardiomyocytes from MI and provides increased vascularity in the post-injury zone to prevent further ischemic tissue damage [35].

**Clinical Trials Using Stem Cells in Acute MI**

Although, multiple experimental animal models and clinical trials of cell-based cardiac therapy have delivered promising results, the mechanisms of their effect are unclear [36]. Clinical trials in humans were aimed at determining whether stem cell therapy could translate into a feasible therapeutic modality.

The majority of large clinical trials used bone marrow stem cells alone, but some trials did use two populations. The TOPCARE AMI [37], REGENT [38] and HEBE [39] trials were ones that used a second cell line in addition to BMCs. Most commonly stem cells were delivered via intracoronary injection and some of the parameters that were assessed for significance were, increase in left ventricular ejection fraction, decrease in end systolic and end diastolic volumes and reduction in infarct size. These parameters were measured by LV angiography, MRI, SPECT or 2D echocardiography.

The first clinical trial performed in humans was published in 2002 by Strauer et al. [40] in Germany. It was a non-randomized trial that studied 10 patients in each arm with one group receiving intracoronary BMCs in addition to the standard therapy for AMI, in the form of PCI. After 3 months of follow-up, left ventriculography showed a significant decrease in the infarct region within the cell therapy group (from 30 ± 13 to 12 ± 7%, P=0.005) and was also significantly smaller compared with the standard therapy group (P=0.04) [40]. They also demonstrated a significant improvement in stroke volume index, left ventricular end-systolic volume, contractility and myocardial perfusion of the infarct region, within the study group. Their group concluded that the marked
therapeutic effect noted in their study could be attributed to BMC-associated myocardial regeneration and neoangiogenesis [41].

The major randomized clinical trials that have shown a benefit in the group given stem cell therapy over the control group are summarized in Table 2. Small to medium sized clinical trials suggest a treatment effect on LVEF within the range of 0-3% when autologous stem cells are harvested and injected approximately one week after an AMI [9].

**Landmark Trials with Promising Findings**

The major trials that have shown significant improvements in EF include the TOPCARE-AMI trial [23] which looked at 59 patients with AMI who were randomly assigned to receive either CPCs or BMCs into the infarct artery at 4.9 ± 1.5 days after AMI that was treated by revascularization with PCI. By quantitative LV angiography at four months, LV ejection fraction (EF) significantly increased (50 ± 10% to 38 ± 10%; p<0.001), and end-systolic volumes significantly decreased (54 ± 19 ml to 44 ± 20 ml; p<0.001), without differences between the two cell groups. Contrast-enhanced magnetic resonance imaging after one year revealed an increased EF (p<0.001), reduced infarct size (p<0.001), and absence of reactive hypertrophy, suggesting functional regeneration of the infarcted ventricles. Having no control group to compare these results to, however, make validity of these findings uncertain.

The REPAIR-AMI trial [42], which has used one of the largest sample sizes so far, randomly assigned 204 patients to receive intracoronary infusion of BMC or a placebo medium 3 to 7 days after successful PCI. Patients with a baseline ejection fraction that was at or below 35% received therapy. By intravascular ultrasound (IVUS). At 6 months, BMC group had a greater absolute increase of global LVEF than placebo group, measured either by angiography (mean+SD increase 7.1±12.3 vs. 1.2±11.5%, P<0.05) or by 2-D echocardiography (mean+SD increase 4.0±11.2 vs. 21.4±10.2%, P<0.03). Overall, they showed a 5% increase in LV function in 6 months over the control group.

The Prochymal® Intravenous Infusion Following Acute Myocardial Infarction (NCT00877903) has completed recruitment of 220 patients. This was a randomized, double-blind, multi-center trial of Ex Vivo cultured adult human mesenchymal stem cells delivered by intravenous infusion following acute myocardial infarction. The primary outcome will be left ventricular end diastolic volume measured by MRI.

In 2008, a systematic review was undertaken by Martin-Rendon et al. [44] and looked at randomized controlled trials of BMSC therapy for AMI, performed up till 2007. Thirteen trials with a total of 811 participants were included. Results showed that overall, stem cell therapy improved LVEF by 2.99% (P=0.0007), LVEF by 4.74 ml (P=0.003), and myocardial lesion area by 3.51% (P=0.004) compared with controls. Subgroup analysis revealed that there was statistically significant difference in LVEF in favor of BMSCs when cells were infused within 7 days following AMI [44].

In a recent Cochrane review of stem cell treatment for AMI thirty three randomized control trials with 1765 participants were evaluated and demonstrated no statistically significant changes in the incidence of mortality or morbidity [45]. However, in short-term follow up there was improvement in LVEF and this was maintained over ensuing 12 to 61 months. Despite the high degree of heterogeneity in the review there was evidence of reduction left ventricular end systolic and diastolic volumes with improvement in global function.

Despite the positive findings seen in the above-mentioned studies, other clinical trials performed failed to show any statistically significant difference between the study and control groups after stem cell implantation. In particular, the REGENT [38] and HEBE [39] trials had large sample sizes of 200 patients each, and both used a second cell line.

**Table 2**

<table>
<thead>
<tr>
<th>Trial Name and Design</th>
<th>Cell Line</th>
<th>Sample Size (n)</th>
<th>Cell Dose</th>
<th>Days to Admin Post MI</th>
<th>Route of Admin</th>
<th>Imaging Modality</th>
<th>Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOPCARE-AMI [23] (2002)</td>
<td>BMC OR CPC</td>
<td>59</td>
<td>BMC: 2.13 ± 75 x 10^6</td>
<td>4.9 ± 1.5</td>
<td>IC</td>
<td>LV angiogram MRI</td>
<td>Increased LVEF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPC: 0.16 ± 12 x 10^6</td>
<td></td>
<td></td>
<td></td>
<td>Decreased ESV</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reduced infarct size (4 months and 1 year)</td>
</tr>
<tr>
<td>BOOST [41] (RCT 2004)</td>
<td>BMC</td>
<td>60</td>
<td>24.6 ± 9.4 x 10^6</td>
<td>4.8 ± 1.3</td>
<td>IC</td>
<td>MRI</td>
<td>Increased LVEF by 6% over control (A1 6 months)</td>
</tr>
<tr>
<td>REPAIR-AMI [42] (RCT 2006)</td>
<td>BMC</td>
<td>204</td>
<td>2.4 ± 1.7 x 10^6</td>
<td>4.3 ± 1.3</td>
<td>IC</td>
<td>LV angiogram MRI</td>
<td>Increased LVEF by 2.5% over control (A1 4 months)</td>
</tr>
<tr>
<td>FINCELL [43] (RCT 2008)</td>
<td>BMC</td>
<td>80</td>
<td>3.6 ± 10^6 (median)</td>
<td>2.6</td>
<td>IC</td>
<td>LV angiogram MRI</td>
<td>Increased LVEF by 5% over control (A1 6 months)</td>
</tr>
</tbody>
</table>

All values are mean ± SD unless stated
Abbreviations: TOPCARE-AMI Trial: Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction Trial; REPAIR-AMI Trial: Reinfusion of Enriched Progenitor Cells and Infract Remodeling in Acute Myocardial Infarction Trial; BOOST Trial: Intracoronary autologous bone-marrow cell transfer after myocardial infarction; RCT: Randomized control trial.
in addition to BMCs. However, when follow up MRIs were performed on the patients in both these studies; there was no significant increase in LVEF as compared to the control groups.

The recently published CADUCEUS [46] Trial primarily assessed safety after intracoronary injection of cardiosphere-derived cells (CDC) in patients after AMI. The primary endpoint of this trial was death at 6 months, arrhythmias, recurrent MI after cell infusion, occurrence of cardiac tumors or of a major adverse cardiac event. By 6 months, none of these end points were noted in either group. "Four patients (24%) in the CDC group had serious adverse events compared with one control (13%; P=0.06). MRI analysis of patients treated with CDCs showed reductions in scar mass (P=0.001), increases in viable heart mass (P=0.001) and contractility (P=0.02), and regional systolic wall thickening (P=0.015)." However, at 6 months, changes in end-diastolic volume, end-systolic volume, and LVEF did not differ between the control and study group.

Some of the landmark studies with equivocal findings are summarized in table 3. There are multiple factors that may have played into such equivocal findings, including the diversity of patient selection, method and dose of stem cells delivery and the imaging used to assess left ventricular function and myocardial perfusion and infarct size.

### The Onward Journey

As a theoretical construct, the concept of using biological engineering techniques to counteract the destructive effects of myocardial infarction is extremely appealing. Furthermore, the use of stem cells appeared to be the answer that was long sought after, when even timely interventions like primary PCI and thrombolytic could not salvage sufficient myocardium in the face of an acute MI.

While some of the clinical trials have shown promising results with respect to recovery of EF and reduction in infarct size, the overall results in several studies have proved essentially equivocal. Similarly, positive animal studies have not been replicated in humans. This leaves much uncharted territory and going forward many questions still need to be addressed. Which cell type and mode delivery works in which clinical setting (acute, sub acute, or chronic), mode of delivery, concentration, and using clinical outcomes rather than surrogates?

Clearly a path has been fashioned for the initiation of further and bolder studies which hopefully will deal with some of these unanswered questions and reveal if the benefits shown in animal models and hinted at in human studies can translate into an accepted standard of practice and improve clinical outcome.

### References