Stem Cell Therapy: A New Approach for Treatment of Myocardial Infarction

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Abstract

Stem cell therapy offers the opportunity of myocardial repair in patients who have suffered a myocardial infarction, a concept currently not feasible with present treatment options. Embryonic, adult, and induced pluripotent stem cells all offer a potential cell source for myocardial repair. Pre-clinical studies suggest that embryonic and induced pluripotent stem cells may be the most ideal cell type as they have the potential to differentiate into cardiomyocytes and restore a degree of functional recovery in animal models. Due to practical and ethical issues surrounding these cell types however, more focus has been on the use of adult stem cells, predominantly those of the bone-marrow. Pre-clinical studies suggest that bone-marrow stem cells can promote a degree of functional recovery through either differentiating into cardiomyocytes or acting in a paracrine manner to promote neoangiogenesis. The apparent success in pre-clinical models paved the way to a number of clinical trials to take place. Although mixed results have been reported, these trials have however shown that stem cell therapy is safe and feasible in humans. Many questions are still unanswered including, what is the optimal cell type, dose and timing of transplantation. This review highlights the benefits and limitations of each cell type and possible regenerative mechanisms.

Introduction

Cardiovascular disease is the leading cause of death in the Western world. In the United Kingdom alone, there are approximately 124,000 cases of myocardial infarction (MI) every year [1].

The main treatment option for these patients is revascularization therapy including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). The aim of such procedures is to restore blood flow to the ischaemic myocardium in a timely manner in an attempt to limit the degree of myocardial damage and subsequent death. However, most patients who suffer an MI display impaired heart function and many go on to develop heart failure as myocardial performance declines, thus requiring additional intervention and hospitalization [2]. Therefore, new cost-effective treatments are urgently needed.

A new treatment strategy that aims to regenerate the damaged myocardium and restore myocardial function is now being sought, with stem cell therapy offering much promise. Embryonic stem cells, adult stem cells, and more recently induced pluripotent stem cells all demonstrate the ability to differentiate into cardiac-lineage cells in vitro [3-5]. As such, many research teams have focused on utilizing these cells as possible sources for myocardial repair in animal models of MI. The apparent success in a majority of these studies has paved the way for a number of human clinical trials to take place in order to translate these findings into the clinic.

This review therefore discusses the use of stem cell therapy in the treatment of MI and focuses on the pre-clinical and clinical studies that have taken place.

Methodology

Literature was obtained using the electronic database PubMed. Search terms used and number of hits used for in this review is summarized in Table 1.

For inclusion, papers must be primary literature, directly related to MI or cardiomyocyte differentiation, and peer-reviewed. Excluded were non-primary literature, studies related to non-myocardial ischaemia, articles in languages other than English, and articles pre-1998.

Pre-clinical studies

Adult cells: Adult stem cells (ASCs) are multipotent cells that have the ability to self-renew and differentiate into any cell type of a

<table>
<thead>
<tr>
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<th>No of Hits</th>
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<tr>
<td>Bone-marrow-derived, stem cells, myocardial infarction, humans, clinical trials</td>
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</tr>
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</table>

Table 1:

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particular organ or system in which they are found. They have been identified in a number of tissues including the bone-marrow, heart, skeletal muscle and adipose tissue. Their use as a cell source for myocardial regeneration has been widely discussed [6-8].

**Foetal cardiomyocytes:** Foetal cardiomyocytes were one of the first cell types to be studied for cardiomyoplasty after MI, predominantly because they are already destined to become adult cardiac tissue, therefore may integrate well with host tissue and successfully restore myocardial function. There have been mixed results when foetal cardiomyocytes have been transplanted into rodent models. Several studies report survival for up to six weeks post-transplant, improvement in left ventricular (LV) function and reduced mortality rates [9,10]. Additionally, some reports suggest that the donor cardiomyocytes are able to successfully integrate into host myocardium [9,11]. In contrast, a number of studies report low survival rates with limited or no integration and no LV improvement [12,13]. Another study suggests that the time of transplant influences the success rate [14]. They reported that the optimal transplantation time is 2-3 weeks post-infarct, when the inflammatory response has resolved but scar formation is limited [14]. Other issues limiting foetal cardiomyocytes include that most transplanted cells remain immature and structurally unorganised, there is a limited source of cells and, as they are non-autologous, present a possibility for immune rejection.

**Skeletal myoblasts:** Skeletal myoblasts (SMs) are a potential autologous cell source for regenerating the infarcted myocardium. They develop from skeletal muscle satellite cells and already have contractile functions. Transplantation of SMs into models of MI showed the capacity of these cells of replacing cardiomyocyte lost and restoring a degree of cardiac function [15-17]. Transplanted SMs appear to be short-lived, with a significant number of transplanted cells no longer detectable after 72 hours post-grafting [18]. Those that survive develop patches of elongated and striated cells that retain skeletal muscle cell characteristics [15], unable to integrate into myocardial tissue, as evidenced by the failure to detect gap junctions between skeletal and myocardial cells [16]. This lack of integration poses the risk of ventricular arrhythmias [19].

**Bone marrow-derived stem cells:** Cells of the bone-marrow and circulation have received much attention as a therapeutic cell source. They include haematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), and mesenchymal stem cells (MSCs).

In 2001 Orlic and colleagues reported the first use of lin/c-kit+ murine HSCs in regenerating the infarcted heart [20]. In vitro expanded HSCs were delivered via intramyocardial injection 3–5 hours after infarct initiation. They reported the presence of proliferating HSC-derived cardiomyocytes, endothelial cells (ECs) and smooth muscle cells (SMCs) occupying around 68% of the infarcted area 9 days post-transplantation, suggesting the ability of HSCs to trans-differentiate into cardiac and vascular-lineage cells [20]. These HSC-derived myocytes expressed connexin-43, suggesting electrical coupling and a degree of functional recovery was observed [20]. A study published in the same year was in line with Orlic’s results in reporting that HSCs migrated to the infarcted myocardium are able to differentiate into cardiomyocytes and ECs thereby contributing to the formation of functional tissue [21]. Additionally, cytokines such as granulocyte-colony-stimulating-factor (G-CSF) and stromal-derived-factor-1α (SDF-1α) have been administered to improve mobilization and recruitment of HSCs to infarcted areas, initiating myocardial repair [22,23]. Many have disputed these results with reports of no trans-differentiation and no functional recovery taking place [24-26], meaning that cell fusion rather than trans-differentiation could be occurring.

EPCs have the potential to regenerate damaged/aged ECs and promote post-natal angiogenesis. The definition of EPC is not homogeneous. Based on antigenic and clonogenic characteristics, three populations, often referred to in the literature, can currently be distinguished: CFU-Hill, also sometimes referred to as CFU-EC, yield adherent colonies consisting of myeloid cells and T-cells. The second population, most commonly used in cardiovascular studies,

is now often referred to as circulating angiogenic cells (CACs) and comprise mainly myeloid cells, who are able to support angiogenesis in a paracrine way. Finally, endothelial colony forming cells (EFC) give rise to cells not expressing myeloid markers anymore, but exhibiting phenotypic and antigenic characteristics of mature ECs. Recent studies showed that EPCs may have greater potential for cell therapy after an MI compared with other cell types [27,28].

The means for utilizing EPCs for MI therapy is to boost their numbers through the administration of cytokines or through their in vitro expansion and re-administration. G-CSF promotes the mobilization of EPCs from the bone-marrow. Many studies have isolated EPCs in vitro from G-CSF-mobilized mononuclear cells harvested from the circulation. When these EPCs have been reintroduced via intravenous, intramyocardial or intracoronary transfer into MI models, they appear capable of enhancing neovascularization, through their differentiation into ECs, leading to improved infarct perfusion [29-31]. As a result, a reduction in cardiomyocyte apoptosis, increased survival of viable myocardium and improvements in myocardial function has been observed [29,30]. Additionally, the use of SDF-1α delivered to the infarct site can further improve EPC homing to the myocardium leading to increased neovascularisation [30,32].

MSCs are also found within the bone-marrow, peripheral and umbilical cord blood, and within tissues including adipose tissue and the adventitia of the vascular wall. They are capable of differentiating into ECs [33] and cardiomyocytes [34], both in vitro and in vivo, and more efficient in restoring myocardial function after MI compared with HSCs [35]. Our recent work shows that pericyte-like progenitor cells from saphenous vein leftovers of CABG patients improve recovery from myocardial infarction trough stabilization of vascularisation, containment of infarct extension and inhibition of fibrosis, by a mechanism involving the microRNA 132 and its target genes of Ras-GTPase activating protein and methyl-CpG-binding protein 2 (Kareta et al., Circ Res in press).

Bone-marrow-derived MSCs have been cultured ex vivo and delivered to the infarcted heart via intramyocardial injection immediately, or shortly following, MI [36-38]. These cells were able to differentiate into ECs and cardiomyocytes and act as potent activators of angiogenesis through releasing VEGF. This led to increased vessel density in the infarct area and a restoration of myocyte mechanical function and overall LV function, as assessed by improved LV ejection fraction (LVEF) and fractional shortening (FS). Similar results are seen when MSCs are transplanted up to 1 week post-MI induction [39]. MSCs can also be mobilized by G-CSF and migrate to the infarcted heart where they can exert their regenerative effects [40,41]. Cytokines may therefore be useful as adjuvant of systemic MSC delivery [42].

Other sources of MSCs have also been investigated for use in myocardial repair. Adipose tissue is acquiring increasing attention as...
an easily obtainable, autologous source of MSCs. When monolayered adipose tissue-derived MSCs were transplanted onto the scarred area 4 weeks post-MI induction, the engrafted sheet grew to form a thick stratum that included blood vessels, undifferentiated cells, and a few cardiomyocytes [43]. The MSC sheet also acted in a paracrine fashion, producing VEGF to promote angiogenesis in the infarcted myocardium. This led to reduced wall thinning of the infarcted area and increased myocardial function [43]. More recently, adipose tissue-derived MSCs have been delivered via intramyocardial injection immediately following MI induction in mouse and pig models [44,45]. Both studies report an increase in vessel density, reduced scar size, and a functional improvement as evidenced by increased LVEF and improved FS. These results suggest that adipose-derived MSCs are just as capable of restoring function after MI as bone-marrow-derived MSCs.

Bone-marrow cells may therefore be capable of promoting myocardial repair after MI by contributing to neovascularisation and cardiomyogenesis, thereby limiting myocardial remodelling and preserving overall function.

Cardiac resident stem cells: The heart was long considered a terminally differentiated organ lacking the capacity to replace or repair its cells. In the last 10 years however this concept is slowly changing with the introduction of the potential of a cardiac resident stem/progenitor cell (CSC). Beltrami’s study was the first to show that isolated c-kit+/Lin- CSCs behave as self-renewing, clonogenic and multipotent cells that give rise to cardiomyocytes, ECs and SMCs [46]. It is thought that these CSCs are activated after heart injury and migrate to damaged regions to generate new cardiomyocytes [47]. More recently, it has been demonstrated that the human heart has a significant growth reserve and replaces its myocyte and non-myocyte compartments several times during a life-time [48]. These studies therefore support the idea that CSCs may be capable of repairing the heart after an MI.

Both murine and human CSCs have been cultured and expanded in vitro and delivered to the infarcted rodent heart by intravenous, intracoronary and intramyocardial injection [46,49-52]. These studies show that CSCs are capable of homing to the ischaemic-damaged heart where they promote increased vessel density, cardiomyocyte differentiation and reduced myocyte apoptosis at the infarct site. This leads to reduced infarct size and attenuation in cardiac remodelling and dysfunction. CSCs are reportedly capable of differentiating into the same cells in situ as can be obtained in vitro [51], therefore there is no need to pre-differentiate these cells prior to transplantation, thus reducing their time in culture. Cardiomyocyte differentiation of transplanted CSCs however seem to be quite low suggesting that the beneficial effects on myocardial function are through paracrine effects on neoangiogenesis and endogenous CSC activation/differentiation rather than their self-differentiation.

Most studies have transplanted CSCs immediately following or within a few hours of MI-onset. As it is more clinically desirable to use autologous CSCs, then delivery at MI-onset is not possible as it takes a number of weeks to expand these cells in culture [53]. The transplantation of autologous CSCs into old infarcts or the activation of endogenous CSCs, without the need for cell transplantation, need to be investigated. Tang delivered CSCs via intracoronary infusion one month after MI-induction [53]. After 35 days, more viable myocardium and reduced fibrosis was observed in non-infarcted regions and improved LV function was reported. Once again there was limited CSC differentiation suggesting a beneficial paracrine effect.

Endogenous CSCs express a number of growth-factor receptors and when their ligands are introduced there is significantly increased endogenous CSC proliferation and migration towards infarcted regions [54-56]. Once there, CSCs are able to differentiate into cardiomyocytes, replacing around 40% of the scar [53] and promote neoangiogenesis. These changes have led to increased myocardial performance and increased animal survival [54], suggesting that stimulating endogenous CSC activation/mobilization may be another treatment option for myocardial repair.

Embryonic stem cells

Embryonic stem cells (ESCs) are pluripotent cells derived from the inner-cell-mass of the blastocyst [57]. Their pluripotent nature means they can differentiate into any cell type of the three germ layers that make up the body, including cardiomyocytes [57]. This characteristic makes ESCs an attractive cell source for cell transplantation therapies for many diseases, including that of myocardial repair.

Murine ESCs have been demonstrated to survive, migrate and proliferate when injected into infarcted rodent myocardium up to one hour post-MI [58-60]. Indeed, these studies also demonstrated the potential of ESCs to provide some, albeit small, restoration of global LV function up to eight weeks post-transplant. One of the concerns to arise from these studies however was that the degree of cardiomyocyte differentiation was extremely low, with reports as low as 0.5% of the total number of cells delivered differentiating towards a cardiomyocyte lineage [59]. An additional issue was the high incidence of teratoma formation with reports of 100% of rats receiving mESCs developing teratomas [59]. These limitations are not confined to murine cells. It is also the case in rodent models receiving human ESCs (hESCs) [3]. When hESCs were injected into both healthy and infarcted myocardium, few cardiomyocytes were detected and teratomas had formed in approximately 50% of rats.

Two key issues have been highlighted that need addressing if ESCs are ever to be used in clinical practise, namely the extremely low rate of cardiomyocyte differentiation and the high incidence rate of teratomas. It is known that the risk of teratoma formation is reduced as cells become more specialised so in theory, if the rate of cardiomyocyte differentiation can be significantly increased, teratoma risk should reduce. Indeed, many research groups are now pre-differentiating ESCs into Nkx2.5+ cardiogenic progenitors (CPCs) or early cardiomyocytes in vitro, through methods such as embryoid-body formation, before transplanting into MI models [3,61]. The incidence of teratomas in these studies is considerably reduced with many reporting a complete absence of tumours [62,63]. When teratomas are present they are on average significantly lesser in volume compared with undifferentiated ESCs [60] and usually occur due to inefficient differentiation protocols, leading to the presence of undifferentiated cells within the transplant media. The majority of studies using mouse and human ESC-derived CPCs or cardiomyocytes have reported at least an attenuation of LV decline in the short term (4-8 weeks) through reducing the occurrence of LV remodelling and improving myocardial contractility [3,61,63,64]. Again, ESC-derived CPCs can survive the infarct environment and differentiate into immature cardiomyocytes expressing a-actinin, cardiac MHC and troponin-I around the infarct boarder-zones [61,64]. There is a possibility that these cells continue, at least for a short time, to proliferate as detected by Ki67 expression [3,62]. These cardiomyocytes are however low in number, small and immature but seem to be able to form gap-junctions between themselves [63]. Whether or not they can form connections...
with host cardiomyocytes is still an area of controversy [65,66]. ESC-derived ECs have also been detected in transplanted hearts [61,67], suggesting a possible angiogenic response that may also contribute to the attenuation in LV decline.

ESCs show promise as a cell source for transplantation therapy after MI. They are capable of differentiating into cardiomyocytes ex vivo that can successfully survive within the infarct area and promote a degree of myocardial functional recovery in MI-models [3,61,64]. They do however come with a few, but key, limitations. The requirement of animal products for ESC culture poses a risk of zoonotic transfer. This can easily be overcome with the development of xeno-free media. Additionally, the low number of cells that can be produced and the inability to control teratoma risk makes them unsuitable for human transplantation therapy at present. Aside from the practical limitations they are surrounded by ethical controversy, mainly concerning the destruction of human embryos in order to harvest such cells. With the availability of ASCs and the discovery of being able to produce induced pluripotent stem cells, whether or not ESCs become part of clinical therapy in the future is far from certain.

**Induced pluripotent stem cells**

In 2006 Yamanaka and colleagues successfully reprogrammed murine somatic cells into a pluripotent ESC-like state by retroviral delivery of the transcription-factors OCT-4, SOX-2, Klf-4 and c-Myc [68]. These new, so called induced pluripotent stem cells (iPS cells), had a similar morphology and up-regulation of gene expression as ESCs, and also gave rise to teratomas consisting of cells of all three germ layers when injected into nude mice, demonstrating their pluripotency.

In 2007 two independent groups showed that iPS cells were able to be produced from human somatic cells [69,70]. These breakthrough experiments opened up the possibility of a new type of cell that can differentiate into any cell type of the body and can be generated from the patient’s own somatic cells, making patient-specific treatment more feasible.

iPS cells can form embryoid-bodies with spontaneously contracting clusters [5] in the same way as ESCs. These contracting clusters have been shown to occur more readily with iPS cells than with ESCs, express cardiac mesoderm and cardiomyocyte markers and demonstrate electrophysiological properties [5]. iPS cell-derived cardiomyocytes display a similar genetic profile to ESC-derived cardiomyocytes [71,72] and demonstrate similar contractile properties, although they are still significantly different in comparison to ventricular tissue of comparable age [73], demonstrating their immaturity.

iPS cells have been assessed as a potential cell source for the treatment of acute MI. Spontaneously contracting embryoid-bodies were produced by the hanging-drop culture method and injected into the myocardium of mouse models 30 minutes after LAD ligation [74]. Over the four week follow-up, mice displayed increased LVEF and FS and a normalisation of systolic wall motion. Sinus rhythm was also maintained throughout with no ventricular tachycardia (VT) or ectopy. These results demonstrated a restoration of contractile performance, LV wall thickness and electrical stability [74]. As with ESCs, iPS cells pose a risk of teratoma formation due to their pluripotent nature. However, this study reported no teratoma formation in immunocompetent mice but did report tumour growth in immunosuppressed mice after subcutaneous injection of iPS cells [74]. Another study transplanted iPS cell-derived cardiomyocytes into acutely infarcted hearts of NOD-SCID mice. Cardiomyocytes were able to survive, showed no marker of pluripotency and did not form tumours [71] suggesting that like ESCs, the more differentiated the cells the less tumour risk they pose.

Research has become focused on boosting iPS-derived cardiomyocyte cell number through more efficient culture and differentiation protocols. A study has recently reprogrammed somatic cells into iPS cells without the use of c-Myc, promoting cardiac mesoderm lineage differentiation [75]. The authors report that c-Myc-dependent reprogramming produces progeny that consistently prolong the expression of Oct-4 and FGF-4 genes whilst suppressing cardiac differentiation. C-Myc-independent reprogramming however led to the up-regulation of pre-cardiac (CxCR4, Flk-1 and Mesp 1/2) and cardiac (NKx2.5, Me2c and myocardin) gene expression. This progeny was reported to undergo early and robust cardiogenesis during in vitro differentiation [75]. Research teams are looking at improving differentiation protocols to generate higher cardiomyocyte cell numbers [76-78]. Key safety issues with iPS cells are the requirement for integrating viral-vectors for genetic reprogramming of somatic cells and the use of animal products in the culture media. A xeno-free culture medium has recently been described that can support human ESCs and iPS cells for prolonged periods of time whilst maintaining their pluripotent characteristics, allowing for the production of clinical-grade cells [79]. In recent years non-integrating viral-vectors [80], drug-inducible transgenic systems [81], transgene removal systems including the Cre-Lox system, non-viral methods [82,83], and even direct reprogramming [84] (removing the need for iPS cell stage) are being developed, however the reprogramming efficiency is low.

iPS cells represent an opportunity for providing patient-specific treatment after MI. iPS-derived cardiac-lineage cells may have potential in restoring myocardial function in a rodent model [74] however the small number of cardiomyocytes being produced with current differentiation protocols needs to be addressed. Efficient cardiomyocyte differentiation methods are essential for developing cardiac cells for regenerative medicine although recently, methods for direct reprogramming [84] may remove the need for acquiring an induced pluripotent phenotype altogether.

**Clinical trials**

ESCs and potentially iPS cells offer the most ideal cell type for myocardial regeneration due to their pluripotent nature but obvious practical, ethical and political issues currently prevent their progress as a clinical tool. Of the adult cells, SMs, bone-marrow-derived stem/progenitor cells, and possibly in the future, cardiac-resident stem/progenitor cells offer the most realistic means of cell-based cardiac regeneration. As such, clinical trials have focused on utilizing autologous SMs and bone-marrow cells.

**Skeletal myoblasts:** The first use of SMs being transplanted into a human patient was reported in 2001 [85]. The patient received injections of SMs in and around the non-viable areas of myocardium immediately following CABG surgery. After 5 months, the patients’ clinical status improved from New York Heart Association (NYHA) class III to II and the LVEF increased from 21% to 30%. Additionally, myocardial contractility improved and no arrhythmias were detected on holter electrocardiogram analysis [85]. These results paved the way for a number of other phase-1 safety and feasibility trials to take place (Table 2).

These phase-1 trials mainly involved a small number of patients that were planned to undergo revascularization surgery. Each trial varied with regards to the number of cells being transplanted (Table

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>No of Patients</th>
<th>No Cells</th>
<th>Undergoing CABG</th>
<th>Delivery Route</th>
<th>Outcomes</th>
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</thead>
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<tr>
<td>[85,89]</td>
<td>1</td>
<td>800x10^4</td>
<td>Yes</td>
<td>IM</td>
<td>NYHA class, LVEF &amp; tissue viability improved. No arrhythmias. Graft survived up to 1.5 years. Cells had skeletal muscle phenotype &amp; aligned in parallel with cardiomyocytes. No connections formed.</td>
</tr>
<tr>
<td>[90,92]</td>
<td>8</td>
<td>871x10^3</td>
<td>Yes</td>
<td>IM</td>
<td>LVEF, tissue viability &amp; contractility, &amp; NYHA score improved. 5 patients developed VT.</td>
</tr>
<tr>
<td>[87]</td>
<td>4</td>
<td>300x10^4</td>
<td>No</td>
<td>IM</td>
<td>&lt;1% myoblast survival, no inflammation, increased vessel density, cells aligned in parallel with myocardium. 4 patients developed arrhythmias.</td>
</tr>
<tr>
<td>[89]</td>
<td>11</td>
<td>221x10^4</td>
<td>Yes</td>
<td>IM</td>
<td>LVEF, tissue viability &amp; contractility, &amp; NYHA score improved. 1 patient developed VT.</td>
</tr>
<tr>
<td>[91]</td>
<td>9</td>
<td>4x10^5-5x10^5</td>
<td>Yes</td>
<td>IM</td>
<td>LVEF &amp; contractility improved. VT observed in first 2 patients (7 patients received prophylaxis).</td>
</tr>
<tr>
<td>[88]</td>
<td>9</td>
<td>1x10^8</td>
<td>No</td>
<td>Percutaneous transcoronary-venous</td>
<td>Limited LVEF improvement. NYHA score improved. VT developed in 1 patient not receiving prophylaxis</td>
</tr>
<tr>
<td>[93] (randomized controlled)</td>
<td>n=12 SMs; n=11 controls</td>
<td>30x10^8-600x10^8</td>
<td>No</td>
<td>Endovascular transcatheter</td>
<td>1 patient in control and 2 patients in treatment group developed VT. NYHA score improved. No effect on myocardial viability or function.</td>
</tr>
</tbody>
</table>

Table-2: Key outcomes of phase-1 safety and feasibility trials with skeletal myoblasts.

2) and the length of follow-up (6-52 months). All trials report the potential of generating millions of cells from a small skeletal muscle biopsy with a myoblast purity consistently >60% and cell viability >90% [86-88] suggesting that it is feasible to generate large quantities of autologous cells for transplantation therapy. The study by Pagani [87] allowed for the analysis of graft success and provides an insight into how myoblasts behave in the human heart. Animal studies suggest that myoblasts are short-lived, maintain their skeletal phenotype and are unable to form connections with host cardiomyocytes [15,16,18]. Pagani reported similar findings, with less than 1% of the 300x10^6 cells transplanted surviving and those that do survive maintain a skeletal phenotype [87]. They do however demonstrate that the majority of surviving myoblasts align themselves in parallel with host myocardial fibres, suggesting the potential for structural enhancement. Further to this, a post-mortem analysis in 2003 of the first patient to receive a myoblast transplant in 2001 revealed that the transplanted cells were unable to form connections with the myocardium but did display a more predominant expression of the slow, rather than the fast, myosin heavy-chain isoform that may allow them to sustain a cardiac workload [89].

Although not designed for looking at the efficacy of myoblast therapy a number of trials reported a significant beneficial effect on LV function, as assessed by a significant increase in LVEF, and an improvement in tissue viability and contractility within the infarct area after intramyocardial delivery [86,90,91]. For example, Menasche reported an increase in LVEF from 23.8% to 32.1% (P<0.02) and 62% of the tissue segments injected with myoblasts, associated with improved viability and contractility in six of the eight patients within the first 12 months [90]. These functional improvements translated to a positive impact in NYHA score (P<0.0001). These factors remained stable for up to 52 months post-transplant [92].

Siminiak [88] and Dib [93] have conducted trials using alternative methods of cell delivery, namely percutaneous trans-coronary-venous and endovascular trans-catheter injection respectively. Through these methods there was limited functional benefit but there was an improvement in NYHA score. The trial by Dib and colleagues was particularly interesting as it is the first randomized, controlled phase-1 trial to have taken place [93]. Additionally, these trials were the first which did not involve patients undergoing revascularization by CABG. Therefore the improvements in tissue viability and function in the previous uncontrolled studies could have been predominantly due to revascularization from the CABG rather than the myoblast transplantation. However it is important to note that many of the revascularization procedures were performed in areas distant from the transplant area.

At present only one randomized, placebo-controlled, double-blind phase-2 trial has taken place. The MAGIC trial [94] incorporated 121 patients with an indication for CABG. Immediately following CABG, myoblasts or placebo solution were injected into non-viable, akinetic patients with an indication for CABG. Immediately following CABG, revascularization procedures were performed in areas distant from the transplant area. At 6 months, tissue viability and global myocardial function was not significantly different between those receiving myoblasts and those receiving placebo [94] suggesting that myoblast transplantation is not related to any significant benefit in the infarcted heart.

One safety issue that has emerged from these trials is the incidence of ventricular arrhythmia. Most studies report a number of patients developing either sustained or non-sustained VT predominantly within the initial post-operative period [87,90,91,93]. Some studies therefore had to adapt the protocol to encompass prophylaxis for the remaining patients on the trials [91]. It is important to consider however that the patients enrolled in these studies are more prone to...
developing arrhythmias. Indeed, the phase-1 randomized trial [93] and phase-2 MAGIC trial [94] report no significant difference between control or cell transplantation groups in VT incidence, however this area still remains a cause for concern.

**Bone-marrow-derived stem cells**

The success of bone-marrow cells to restore a degree of functional recovery in animal models of MI has been followed by a strong concentration of clinical trials. As with pre-clinical studies, the majority of trials have taken the form of collecting and re-introducing bone-marrow mononuclear cells (BMNCs) into the heart, or the mobilization of endogenous BMNCs by lone G-CSF therapy.

G-CSF is a non-specific stimulant of cell mobilization from the bone-marrow. In animal models it has successfully been used to stimulate bone-marrow stem/progenitor cell mobilization into the circulation [22,40]. These cells appear to be capable of restoring function by differentiating into cardiomyocytes and/or stimulating neoangiogenesis [29,34].

In clinical studies to date, subcutaneous G-CSF administration has successfully led to significant increases in circulating CD34+ cells and leukocytes from the patient’s bone-marrow with only occasional mild side-effects [95-99] (Table 3). An early phase-1, non-randomized, trial incorporating 23 patients reported a significant improvement in wall motion score (WMS) and myocardial perfusion in the treatment group verses controls at 3 months (P<0.0001 for both) [100]. Additionally, there was a trend towards increased LVEF in the treatment group, although this did not reach significance [100]. Similar results were reported in the larger FIRSTLINE-AMI randomized, controlled trial involving 50 patients. LVEF, WMS, and tissue viability all significantly improved in the treatment group after 6 months [96]. These results suggest that CD34+ cell mobilization by G-CSF administration could promote a degree of functional recovery after MI in humans. These trials however are small in number and could not evaluate the efficacy of the therapy, but only determine the safety and feasibility of mobilizing BMNCs with G-CSF in patients after an MI. These positive results therefore should be viewed with caution as many other small trials report no clinical benefit [101,102].

A number of randomized, placebo-controlled phase-2 trials have reported no significant benefit of lone G-CSF treatment. The REVIVAL-2 trial reported no significant improvement in LVEF and no significant reduction in overall infarct size in the treatment group between baseline and 4-6 months follow-up [98]. The double-blind, randomized, placebo-controlled G-CSF-STEMI [102] and STEMMI [99] trials report similar results (Table 3), suggesting that BMNC mobilization alone is not enough to evoke a clinically significant recovery in humans. Further larger, randomized, double-blind, placebo-controlled trials are therefore required.

Many more trials have centred on re-introducing autologous BMNCs through direct intramyocardial/intracoronary transfer. Although more invasive, these methods allow for the full complement of cells to reach the damaged myocardium as compared with the widespread, systemic mobilization gained through G-CSF alone.

Most studies have focused on acute myocardial infarction (AMI) and vary with regards to BMNC numbers, patient baseline characteristics and length of follow-up. Many trials demonstrate safety and feasibility of BMNC transplantation by intracoronary or intramyocardial transfer [103-108], however the clinical and functional improvement is far from clear with mixed results being reported [103,105,107,109].

The randomized, controlled TOPCARE-AMI trial reports that intracoronary infusion of either BMNCs or blood-derived progenitors 4 days post-AMI leads to significant improvements in global LVEF and WMS at the infarct border-zone from baseline to 4 months follow-up, a response that significantly differed from the control group [106].

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Design</th>
<th>No of Patients</th>
<th>G-CSF Dose (μg/kg/day)</th>
<th>Treatment Initiated</th>
<th>Follow-Up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>[95] (MAGIC Trial)</td>
<td>Phase-2, Randomised, Controlled</td>
<td>n=7 BMNC; n=3 GCSF only; n=1 control</td>
<td>10 for 4 days</td>
<td>4 days prior to PCI</td>
<td>6 months.</td>
<td>GCSF treatment is safe. Increased CD34+ cell mobilization. BMNC transplantation significantly increased EF &amp; ESV. Trial stopped due to significant restenosis rate.</td>
</tr>
<tr>
<td>[100]</td>
<td>Non-randomised, Open-labelled</td>
<td>n=14 GCSF; n=9 control</td>
<td>10 for 7 days</td>
<td>48 hours post-PCI</td>
<td>3 and 12 months.</td>
<td>GCSF is safe. Increased CD34+ cells leukocytes. Trend towards increased EF and significant increase in WMS &amp; perfusion vs. control.</td>
</tr>
<tr>
<td>[98] (FIRSTLINE-AMI trial)</td>
<td>Randomised, Controlled</td>
<td>n=25 GCSF; n=25 control</td>
<td>10 for 6 days</td>
<td>90 minutes post-PCI</td>
<td>6 months.</td>
<td>GCSF is safe. Increased CD34+ cell mobilization. EF, WMS &amp; viability significantly improved vs. control. 4 &amp; 5 patients in GCSF &amp; control had restenosis, respectively.</td>
</tr>
<tr>
<td>[101]</td>
<td>Randomised, placebo-controlled</td>
<td>n=8 BMNC; n=8 control</td>
<td>5 for 4 days</td>
<td>37 hours post-PCI</td>
<td>6 months.</td>
<td>GCSF is safe. Increased mobilization of CD34+ cells. No significant benefit with lone GCSF.</td>
</tr>
<tr>
<td>[102] (G-CSF-STEMI Trial)</td>
<td>Phase-2, Randomised, double-blind, placebo-controlled</td>
<td>n=19 GCSF; n=21 control</td>
<td>10 for 5 days</td>
<td>32 hours post-PCI</td>
<td>3 and 6 months.</td>
<td>GCSF is safe. Increased CD34+ cells. No functional benefit with lone GCSF. No difference if restenosis rate vs. control.</td>
</tr>
<tr>
<td>[98] (REVIVAL-2 Trial)</td>
<td>Randomised, Placebo-controlled</td>
<td>n=56 GCSF; n=58 control</td>
<td>10 for 5 days</td>
<td>4-6 days post-PCI</td>
<td>4-6 months. Angiography at</td>
<td>GCSF is safe. Increased CD34+ cells. No functional benefit with lone GCSF. No difference in restenosis rate.</td>
</tr>
<tr>
<td>[99] (STEMMI Trial)</td>
<td>Phase-2, randomised, double-blind, placebo-controlled</td>
<td>n=33 GCSF; n=37 control</td>
<td>10 for 6 days</td>
<td>10-60 hours post-PCI</td>
<td>6 months.</td>
<td>GCSF is safe. Increased CD34+ cells and MSCs. No functional benefit with lone GCSF. No increase in restenosis rate with GCSF.</td>
</tr>
</tbody>
</table>

GCSF granulocyte-colony-stimulating-factor; EF ejection fraction; WMS wall motion score; PCI percutaneous coronary intervention; BMNC bone-marrow mononuclear cells; MSC mesenchymal stem cell

**Table 3: Summary of trials utilizing G-CSF to mobilize bone-marrow cells for treatment of MI.**
There was also a significant improvement in myocardial viability within the infarct area and a normalization of coronary-flow-reserve (CFR) in the infarct-related-artery in patients without restenosis. These initial reports were based on the first 20 patients enrolled, although when 59 patients were followed-up to 1 year there was also a significant improvement in LVEF and infarct size compared with the controls [106]. The results of this small trial suggest that BMNCs have the potential to significantly improve vessel and myocardial function after AMI.

The BOOST randomized, controlled trial support the observation that BMNCs can significantly improve LVEF and WMS up to 6 months [105]. When followed up to 18 months and 5 years however, the initial increase in LVEF could no longer be detected [109], suggesting that any functional benefit resulting from BMNC transplantation is short-lived.

The larger, randomized, double-blind, placebo-controlled REPAIR-AMI trial involving 202 patients found that global LVEF significantly increased at 4 months versus baseline after intracoronary infusion of either BMNCs or placebo [101]. The absolute change in LVEF however was significantly greater in the BMNC group versus the control (P=0.01). The same pattern was found with regards to myocardial contractility but no significant changes were observed in end-systolic volume (ESV) or end-diastolic volume (EDV) in either the control or treated groups at 4 months [103]. A small sub-study associated with the REPAIR-AMI trial also suggests that BMNCs can normalize CFR in the infarct-related-artery and reduce microvascular resistance, in agreement with the TOPCARE-AMI trial, leading the authors to believe that BMNCs may promote vascular repair [110].

The REGENT trial, another large randomized controlled trial, also reported a significant increase in LVEF in the BMNC group however found no significant difference in absolute change in LVEF between any of the treatment groups or controls at 6 months [111] which is in contrast to the previous trials.

An interesting find from both the REPAIR-AMI [103,104] and REGENT [111] trials is that there appears to be significantly greater improvement in LV function with cell therapy in patients with worse baseline LVEF scores. The REPAIR-AMI trial also report a progressive increase in BMNC-associated recovery of contractile function as the interval between reperfusion therapy and time of BMNC infusion increases (P=0.01), with the greatest results seen in those treated >4 days after infarct reperfusion [103,104]. The REGENT trial however found no such association [111].

No major adverse cardiac events (MACE) have been reported with intracoronary infusion in any of the trials discussed, suggesting that intracoronary infusion is safe. In fact, the REPAIR-AMI trial reported that the number of deaths, recurrent MI and revascularization was significantly lower in the treatment group versus control [103,104]. Additionally the combination of deaths, recurrent MI and hospitalisation for chronic heart failure (CHF) occurred less frequently in the treatment group.

Large, randomized, placebo-controlled, double-blind, multicentre trials are therefore warranted in order to clarify the functional and clinical effects of BMNCs after AMI. A trial of this kind has been awarded by the EU-FP7 and is going to recruit 3,000 patients in 17 clinical centres across Europe (the BAMI consortium). (Table 4)

Only a small number of trials have involved patients with CHF as a result of MI (Table 5). The largest trial to date is the STAR-heart study which enrolled 391 patients [112]. BMNCs were delivered via intracoronary infusion into the infarct-related-artery of each patient in the treatment group and followed-up for 5 years. No adverse events were associated with the procedure and at 3 months the treatment group displayed a significant increase in LV function and contractility, leading to a considerable improvement in exercise performance and NYHA score [112]. These improvements appear to be long-standing with the beneficial effects lasting up to five years, whereas LV function in the control group steadily declined. A more clinically important

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Study Design</th>
<th>No of Patients</th>
<th>Cell Dose</th>
<th>Procedure Time</th>
<th>Follow-Up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>[105,119] (TOPCARE-AMI Trial)</td>
<td>Randomized, controlled</td>
<td>n=29 BMNC; n=30 CPC; n=11 Control</td>
<td>7.35±7.31x10⁶ CD34⁻/CD45⁻ Cells</td>
<td>~4 days post-AMI</td>
<td>4 months &amp; 1 year</td>
<td>Cell therapy significantly improved LVEF and WMS at border-zone. No significant difference between cell therapy groups. CFR normalized and viability in infarct-zone significantly increased with cell therapy. At 1 year LVEF and infarct size significantly improved with cell therapy.</td>
</tr>
<tr>
<td>[105,109] (BOOST Trial)</td>
<td>Randomised controlled</td>
<td>n=30 BMNC; n=30 Control</td>
<td>24.6x10⁶ nucleated cells, 9.5x10⁶ CD34⁻ cells, 3.6x10⁶ haemopoietic colony-forming cells</td>
<td>~5 days post-AMI</td>
<td>6 Months and 5 years</td>
<td>LVEF and WMS at border-zone significantly improved in BMNC group vs. controls at 6 months. EDV, ESV, LV mass index and myocardial injury did not significantly differ from control. No significant difference in MACEs or restenosis at 5 years. No significant improvement in LVEF at 5 years.</td>
</tr>
<tr>
<td>[103,104,110] (REPAIR-AMI Trial)</td>
<td>Randomized, double-blind, placebo-controlled, multicentred</td>
<td>n=101 BMNC; n=101 Control</td>
<td>238±174x10⁶</td>
<td>3-7 days post-PCI</td>
<td>4 months &amp; 1 year</td>
<td>Significant improvement in LVEF and regional contractility in control and BMNC groups. Absolute change in LVEF significantly greater in BMNC vs. control. Inverse relationship between baseline and absolute change in LVEF in treatment group. Trend for increased contractile function in patients treated &gt;4 days post-PCI. CFR normalized and vascular resistance decreased in treatment group. No MACEs at 1 year.</td>
</tr>
<tr>
<td>[111] (REGENT Trial)</td>
<td>Randomised controlled, multicentred</td>
<td>n=80 CD34⁺/CXCR4⁺ cells; n=80 BMNC; n=40 control</td>
<td>1.90x10⁹ CD34⁺/CXCR4⁺ cells; 1.78x10⁹ BMNC</td>
<td>7 days post-PCI</td>
<td>6 Months</td>
<td>Procedure is safe. No significant difference in absolute change in LVEF or EDV and ESV between groups. Inverse correlation between baseline LVEF and its change after cell therapy in patients treated with CD34⁺/CXCR4⁺ cells but not with BMNCs. Significant improvement in patients receiving any cell therapy when baseline LVEF &lt;median. No significant difference in MACEs or restenosis between groups.</td>
</tr>
</tbody>
</table>

Table 4: Summary table of key trials utilizing direct transplanation of BMNCs in AMI.
finding was the mortality rates in the treatment group significantly reduced and was significantly less than the control group at 5 years (0.75% per year in the treatment group vs. 3.68% for controls, P<0.01) [110].

Recently however, the randomized, blinded, controlled FOCUS-HF study involving 20 patients receiving BMNCs via transendocardial injections reported no significant difference in LV function with cell therapy at 6 months [113]. Despite this, there were improvements in Canadian Cardiovascular Society (CCS) score, quality of life scores, and a trend towards an increase in myocardial viability and reduced infarct size. An additional aspect of this study looked at the characteristics of patients BM-cells. They found that this patient population showed reduced progenitor cell activity and patients <60 years had significantly increased MSCs (P=0.04) with greater proliferative capacity versus those >60 years [113], suggesting that the presence of chronic infarcts and increasing age leads to BM-cell dysfunction. This may explain the lack of any significant functional benefit in these patients.

A main safety concern with BMNCs is the potential contribution of these cells to atherosclerotic lesions. Indeed, the MAGIC trial was suspended early on due to the unacceptable high occurrence of restenosis in the infarct-related-artery of the two treatment groups [95], although cell therapy was initiated prior to PCI rather than after (Table 3). The majority of other trials however report no significant difference in restenosis rate between cell treatment groups and controls. A recent study looking for evidence of accelerated atherosclerosis with BMNC therapy has also reported no significant difference in maximal stenosis area and plaque volume from baseline to 9 months in BMNC-treated patients or in minimum lumen diameter and percentage of stenosis in the infarct-related-artery in those treated with BMNCs versus controls [114].

As there are a number of different cell types within the BMNC preparations, a number of teams are now isolating and expanding specific stem/progenitor cells, such as antigenically purified or functionally enriched HSCs or MSCs, before reintroducing them to the damaged heart [115,116]. Many of these trials are reporting that this therapy is safe and feasible, with the potential of having a beneficial functional effect in patients with both AMI and CHF [115-118] and therefore may be a safer and more beneficial option over BMNC transplantation. As pre-clinical studies suggest that MSCs, EPCs and HSCs all have therapeutic potential it is important that the most appropriate cell for promoting myocardial repair is identified and expanded to satisfactory numbers. At present, most appealing are MSCs as they can be isolated from easily-obtainable tissues, such as adipose tissue, and have the potential to differentiate into cardiomyocytes and promote neoangiogenesis in the infarcted heart.

### Pathways to go

The number of patients who underwent cell therapies to date is still in the order of thousands. Thus, although researchers have been investigating adult SCs since the 1940’s and bone marrow transplants were introduced 50 years ago, the concept of cell therapy remains new. Since science cannot establish if any type of cell is therapeutically better than another one, research on all kinds of cell therapy should continue. In fact, this is a field where translational innovativeness overwhelms the common concept of scientific originality. Too many breakthroughs discoveries are dropped after publication with no further development toward clinical application. Intellectual property is certainly an issue to consider when making a strategic plan to develop those seminal discoveries.

### Conclusions

Stem cell therapy offers an opportunity to replace/regenerate the damaged myocardium and promote a significant functional recovery after MI, therefore preventing the decline into heart failure.

ESCs and iPS cells offer a potential pluripotent cell source for transplantation therapy after an MI for the future. They are capable of differentiating into cardiac-lineage cells in vitro which upon transplantation into MI models, can contribute to the restoration of
myocardial function through possible angiogenic and cardiomyogenic processes. They are however hampered by the low rate of cardiomyocyte differentiation, the potential for tumour formation, and in the case of ESCs the ethical controversy surrounding their use. These issues, among others, are currently being targeted by many research groups in an attempt to progress these cells into a realistic option for cell therapy.

ASCs, particularly bone-marrow-derived stem/progenitor cells, offer the most realistic source for cell therapy after MI in the near future. Many pre-clinical studies using cells, such as MSCs, demonstrate a potential angiogenic effect in the infarcted heart and possibly the ability to differentiate into cardiomyocytes and ECs. These effects have translated into a degree of functional recovery in animal models and as such a strong concentration of clinical trials utilizing autologous BMNCs has followed. Unfortunately these benefits observed in the pre-clinical studies have not translated into the clinical trials with mixed results being reported. This may be due to wide variation in study design and it is clear that larger, randomized, placebo-controlled trials are indicated. A consensus in terms of the ideal cell dose, time and method of delivery is also mandatory.

References


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