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REVIEW

Bone marrow mononuclear cells and acute myocardial infarction

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Abstract

Stem cell transplantation is emerging as a potential therapy to treat heart diseases. Promising results from early animal studies led to an explosion of small, non-controlled clinical trials that created even further excitement by showing that stem cell transplantation improved left ventricular systolic function and enhanced remodelling. However, the specific mechanisms by which these cells improve heart function remain largely unknown. A large variety of cell types have been considered to possess the regenerative ability needed to repair the damaged heart. One of the most studied cell types is the bone marrow-derived mononuclear cells and these form the focus of this review. This review article aims to provide an overview of their use in the setting of acute myocardial infarction, the challenges it faces and the future of stem cell therapy in heart disease.

Introduction

Despite the recent advances in percutaneous intervention, drug and device therapy, patients with acute myocardial infarction (AMI) and resulting left ventricular impairment have 13% mortality at 1 year [1]. Following the loss of over one billion cardiomyocytes in a functionally significant MI, the overloaded surviving cardiomyocytes undergo abnormal remodelling, eventually leading to heart failure. This condition, a leading cause of death and disability in the developed world, is associated with 5-year mortality rates of up to 70% in symptomatic patients [2]. Current conventional therapies do not correct underlying defects in cardiac muscle cell number [3].

The only therapeutic option that currently addresses cardiomyocyte loss is heart transplantation. However,

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due to stringent selection criteria and chronic shortage of donor hearts, the vast majority of patients are deemed unsuitable or never receive a transplant. Therefore, preventing this progression post-MI is a major challenge requiring novel therapeutic strategies such as stem cell transplantation to improve the prognosis and quality of life for these patients.

The traditional view that the heart is a terminally differentiated organ has been challenged by the discovery of differentiation of stem cells into cardiomyocytes in animal and human hearts [4-7]. This in turn has led to the exciting possibility for regenerative therapy for cardiomyocyte loss after a MI. The demonstration of functional recovery of myocardium through cardiomyogenesis and neoangiogenesis in AMI in murine models by Orlic and colleagues [8] generated tremendous interest in the potential of bone marrow-derived stem cells. Since then, the cardiomyogenic ability of these cells has been challenged. However, studies continue to demonstrate improvement in cardiac function and reduction in infarct size. It should be noted that progenitor cells also contribute to cardiac repair by mechanisms beyond the growth of new cardiomyocytes and as such may offer an 'indirect' benefit.

Animal and human trials

The most promising and obvious cell type for the growth of new cardiomyocytes is the embryonic stem cell; however, considerable technical and ethical issues exist with these cells, which must be overcome before their successful use in humans. Adult stem cells are an attractive option to explore for transplantation as they are autologous, but their differentiation potential is more restricted than embryonic stem cells. Currently, the major sources of adult cells used for basic research and in clinical trials originate from the bone marrow. The bone marrow mononuclear subset is heterogeneous and comprises mesenchymal stem cells, haematopoietic progenitor cells and endothelial progenitor cells. The differentiation capacity of different populations of bone marrow-derived stem cells into cardiomyocytes has been studied intensively. The results are rather confusing and difficult to compare, since different isolation and identification

methods have been used to determine the cell population studied. To date, only mesenchymal stem cells seem to form cardiomyocytes, and only a small percentage of this population will do so *in vitro* or *in vivo*. Pragmatically, the translation of the basic science into clinical research has followed a common pathway: injection of bone marrow-derived mononuclear cells (BMMNCs) as a source of stem cells into the heart. Table 1 provides a summary of clinical trials using BMMNCs in patients with acute MI.

Trials with no sham bone marrow harvest or intracoronary re-infusion in the control group

In the first human trial, Strauer and colleagues [9] re-infused intracoronary BMMNCs 7 days after myocardial infarction (MI). The mean number of mononuclear cells was 2.8×10^7. There was a significant improvement in myocardial perfusion and a reduction in the infarct region in the cell therapy group. The Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) investigators randomised patients into intracoronary infusion of BMMNCs or *ex vivo* expanded circulating progenitor cells 4 days after MI [10]. There was a significant improvement in global and regional left ventricular (LV) function in both groups and a beneficial effect on the post-infarction remodelling process manifest by a profound improvement in wall motion abnormalities in the infarct area and a significant reduction in end-systolic LV volume at 4 months post-MI. The LV ejection fraction (LVEF) further improved at 12 months, resulting in a total increase of 9.3% at 1 year [11]. Of interest, there was no difference between the two active treatment groups. The mean number of infused cells was 245×10^6, which contained haematopoietic progenitor, mesenchymal and stromal cells. However, a major limitation of both of these trials was the lack of a control group receiving sham bone marrow harvest or intracoronary re-infusion.

Another trial in which there was no sham procedure is the Autologous Stem-Cell Transplantation in Acute Myocardial Infarction (ASTAMI) trial, which included only patients with acute anterior MI. The intracoronary re-infusion of BMMNCs 4 to 8 days after infarction did not have a beneficial effect on LVEF compared to percutaneous coronary intervention (PCI) alone at 6 months [12]. This lack of beneficial effect may be explained by the different cell processing protocols used in this trial. Cell processing protocols may have a significant impact on the functional capacity of bone marrow-derived stem cells [13]. Comparison of different isolation protocols revealed a vastly reduced recovery of mononuclear cells and nullification of the neovascularisation capacity when the ASTAMI cell isolation and storage protocol was used [13].

The Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) trial, a slightly larger trial, included 60 patients that were randomised to receive intracoronary BMMNCs or standard therapy 4.8 days after successful PCI following AMI. There was a significant improvement in global LVEF in the cell treatment group at 6 months without an effect on LV remodelling [14]. However, this improvement was not maintained at 18 months. The mean number of bone marrow cells that were infused contained 9.5×10^6 CD34$^+$ and 3.6×10^6 haematopoietic colony-forming cells. The improvement in LVEF did not correlate with the number of CD34$^+$ cells or haematopoietic colony forming cells. Again, a major limitation of the BOOST trial is that the control group did not undergo a sham bone marrow harvest or intracoronary infusion.

The first long-term study involving 62 patients who underwent intracoronary BMMNC transplantation 7 days post-AMI not only resulted in an early significant improvement in ejection fraction (EF) and infarct size, but there was also a significant reduction in mortality and improvement in exercise capacity compared to controls at 5 years [15].

Randomised controlled trials

The Transcatheter Transplantation of Stem Cells for Treatment of Acute Myocardial Infarction (TCT-STAMI) trial, which included a control group receiving a placebo infusion, showed a significant (approximately 5%) improvement in LVEF of patients receiving intracoronary BMMNCs at 6 months [16].

Intracoronary bone marrow derived progenitor cells in acute infarction (REPAIR-AMI), a large randomized double-blind controlled trial that included over 200 patients, showed an improvement in the primary endpoint in the treatment group that was an absolute change in global LVEF from baseline to 4 months, as measured by quantitative left ventricular angiography [17]. Furthermore, the pre-specified cumulative end-point of death, MI, or revascularisation was significantly reduced, and this benefit was maintained at one year follow-up [18]. The mean increase in LVEF in the BMMNC group was 2.5% and there was an inverse relationship between the baseline EF and the degree of improvement. For example, patients with a baseline EF below the median value (48.9%) had an absolute increase in global EF that was three times higher than that in the placebo group. In contrast, the improvement in LVEF in patients with a baseline EF that was above the median value was non-significant (0.3%). The timing of cell infusion post-PCI also had an effect on the primary endpoint. Patients in whom the cells were infused ≥5 days post-PCI were the only ones who derived benefit.

Table 1. Clinical trials using autologous bone marrow mononuclear cells in patients with acute myocardial infarction

Study	Study design	Cell type	Delivery method	Timing post-infarction	Adjunct procedure	Outcome
Meluzin *et al.* [93]	RCT	BMMNC	IC	5-9 days	PCI	Dose-dependent improvement of regional myocardial function by PET
Fernandez-Aviles *et al.* [94]	NR	BMMNC	IC	13.5 ± 5.5 days	PCI	Decrease in end systolic volume, improvement in regional and global function
Janssens *et al.* [19]	RCT	BMMNC	IC	1 day	PCI	No effect on global LVEF, but may favourably affect infarct remodelling
Lunde *et al.* [12] (ASTAMI)	RCT	BMMNC	IC	6 days	PCI	No effect on global LVEF
Schächinger *et al.* [17] (REPAIR-AMI)	RCT	BMMNC	IC	3-7 days	PCI	Improvement in global LVEF
Ge *et al.* [16]	RCT	BMMNC	IC	Immediately	PCI	Improvement in LVEF
De Lezo *et al.* [95]	RCT	BMMNC or GCSF	IC	7 days	IV fibrinolytics + PCI	Improvement in LVEF
Zhan-quan *et al.* [96]	NRC	PBSC	IC	6 days	PCI	Improvement in LVEF
Wollert *et al.* [14] (BOOST)	RCT	BMMNC	IC	4.8 days	PCI	Improvement in LV systolic function
Lipiec *et al.* [97]	RCT	BMMNC	IC	4-11 days	PCI	Improvement in myocardial perfusion with no effect on global LVEF
Huikuri *et al.* [98] (FINCELL)	RCT	BMMNC	IC	2-6 days	IV thrombolysis + PCI	Improvement in global LVEF
Kang *et al.* [99]	RCT	PBSC and GCSF	IC		PCI	Improvement in myocardial perfusion and systolic function
Assmus *et al.* [10] (TOPCARE-AMI)	NR	BMMNC or CPC	IC	3-7 days	PCI	Improvement in LVEF
Schächinger *et al.* [11] (TOPCARE-AMI)	NR	BMMNC or CPC	IC	3-7 days	PCI	Improvement in EF
Strauer *et al.* [9]	NRC	BMMNC	IC	5-9 days	PCI	Reduction in infarct region
Bartunek *et al.* [100]	NRC	BMMNC (CD133)	IC	11.6 days	PCI	Improvement in LVEF
Hirsch *et al.* [21]	RCT	BMMNC	IC	3-8 days	PCI	No effect on global or regional LV function
Tendera *et al.* [20]	RCT	BMMNC	IC	3-12 days	PCI	No significant improvement in LVEF
Chen *et al.* [101]	RCT	BMMNC	IC	18 days	PCI	Improvement in LVEF
Yousef *et al.* [15] (BALANCE)	NRC	BMMNC	IC	7 days	PCI	Improvement in LVEF, exercise capacity and mortality

Time from myocardial infarction to transplantation and outcomes measured are listed. ASTAMI, Autologous Stem-Cell Transplantation in Acute Myocardial Infarction; BMMNC, bone marrow-derived mononuclear cell; BOOST, Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration; CPC, circulating progenitor cell; EF, ejection fraction; GCSF, granulocyte-colony stimulating factor; IC, intracoronary; IM, intramyocardial; LVEF, left ventricular ejection fraction; NR, non-randomised; NRC, non-randomised with control group; PBSC, peripheral blood stem cell; PCI, percutaneous coronary intervention; PET, positron emission tomography; RCT, randomised controlled trial; REPAIR-AMI, Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction; TOPCARE-AMI, Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction.

By contrast, the LEUVEN-AMI study by Janssens and colleagues [19] showed that intracoronary re-infusion of BMMNCs within 24 hours of reperfusion was associated with a greater reduction in infarct size and improved regional systolic function, but no overall improvement in global left ventricular function compared to controls.

Trials that used two different cell populations
More recently, the Myocardial Regeneration by Intra-coronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction (REGENT) trial, which included patients with anterior MI, uniquely compared two cell types. Patients were randomized to receive intracoronary infusion of unselected (n = 80) or selected CD34$^+$CXCR4$^+$ (n = 80) BMMNCs, or to the control group (n = 40) [20]. Although patients in the treatment group had a 3% improvement in LVEF, this did not reach statistical significance. However, the primary endpoint analysis included <60% of the total population of patients, which is likely to be responsible for the failure in the improvement in LVEF to achieve statistical significance. Subgroup analysis showed that baseline EF below the median value (37%) was an independent predictor of significant (≥5%) increase in LVEF after treatment with BMMNCs.

The HEBE trial compared the intracoronary infusion of BMMNCs or mononuclear peripheral blood cells to standard therapy alone following an AMI [21]. The intracoronary BMMNCs were delivered between 3 to 8 days after AMI. They showed no effect of either treatment on regional or global left ventricular function.

Benefits beyond ejection fraction

A recent comprehensive systematic review that included 13 trials with a total of 811 patients showed an improvement in LVEF by 2.99% in the BMMNC group compared to standard reperfusion therapy [22].

A previous meta-analysis by Lipinski and colleagues [23] that included 10 trials with AMI showed that intracoronary stem cell therapy (within the first 14 days after infarction) was associated with a small but significant (3.0%) improvement in LV systolic function compared to standard medical therapy. It was also associated with a non-significant reduction in death and re-hospitalisation from heart failure. Although they found no significant association between the benefits of intracoronary cell injection and the number of injected cells, there was a trend toward a statistically significant association with the injected volume, suggesting the possible presence of a dose-response relationship. The improvement in LVEF was observed in both bone marrow and peripheral mononuclear cells. Similar conclusions were reached in the meta-analysis by Abdel-Latif and colleagues [24], which included 18 studies and showed that stem cell therapy significantly increased LVEF by 3.66%.

In contrast to animal models, the improvement in LV function in most clinical trials is at best modest. However, it should be noted that several of our established therapies that have an impact on prognosis in patients with MI and a reduced LV function, such as angiotensin-converting enzyme inhibitors, β-blockers [25], thrombolytic therapy and percutaneous coronary intervention [26,27], are associated with similar improvements in LVEF. It is likely that adult stem cells exert their benefit on cardiac remodelling through an 'indirect' paracrine effect, and that the small functional benefit seen with this therapy may translate into significant long-term improvement in exercise tolerance and survival [15].

The main surrogate markers used as an end-point have been EF and perfusion defects, which correlate poorly with prognosis and quality of life [28,29]. Therefore, in the future, the validation of progenitor cell therapy for clinical use may depend on the demonstration of a benefit with regard to clinical outcomes such as improvement in prognosis, quality of life [30], New York Heart Association functional classification and exercise capacity.

The debated hypothesis

The divergent findings from current trials may be due to several factors. There appears to be an inverse relationship between the benefit seen with stem/progenitor cell therapy and the baseline LV function, with cell therapy being most effective in patients with a lower LVEF [17,20]. Furthermore, patients with longer ischaemic time (>5 hours) may be more likely to have significant improvement of LVEF following the BMMNC infusion [20].

The timing of cell infusion may also play a role on the derived benefit. Although the REPAIR-AMI trial suggests that the enhanced improvement of the LVEF was confined to patients who were treated ≥5 days after primary PCI, the investigators of the HEBE and REGENT trials showed no interaction between the timing of cell infusion and derived benefit. The meta-analysis by Martin-Rendon and colleagues [22], however, showed that the benefit of stem cell therapy was even greater when the BMMNCs were infused >7 days after MI. The effect of timing on the beneficial effects of BMMNC administration is further supported by the study by Lai and colleagues [31] that showed that intracoronary BMMNC administration provided cardio-protection in a fashion similar to ishaemic preconditioning. This benefit was only seen when the myocardium had not been preconditioned by other means. An ongoing study at our centre, the REGENERATE-AMI (ClinicalTrial.gov NCT00765453), is designed to study the delivery of BMMNCs at very early time points (within 6 hours of PCI). The purpose of this design is to replicate the animal models where very early interventions lead to a significant (40%) improvement in cardiac function [8].

The dose of infused BMMNCs has varied between different trials with variable results. There appears to be a dose-dependent improvement in EF, with the benefit of BMMNCs only seen when doses higher than 10^8 are administered [22].

Direct (transdifferentiation) and indirect (paracrine and angiogenesis) effects of stem cells

To date, there is no direct clinical evidence that cellular cardiomyogenesis in fact occurs in the human heart after transplantation of progenitor cells, and over the past few years, various experiments using different types of stem cells have shown that <2% of the transplanted cells transdifferentiate into cardiomyocytes [32]. Therefore, the number of cardiac cells produced by cardiac regeneration alone is unlikely to explain the effects seen. In experiments using a mouse model of MI, bone marrow-derived cells were shown to undergo a very low level of transdifferentiation into cardiomyocytes and most of these cells continued to differentiate along the haematopoietic lineage [33,34]. However, engraftment of these haematopoietic

cells at the infarct site led to an improvement in myocardial function that is likely attributed to vasculogenesis, angiogenesis and a paracrine effect. Adult stem cells secrete a variety of cytokines, chemokines, and growth factors that are involved in cardiac repair [35] and the production of these factors is increased in response to the hypoxic stress associated with AMI [36]. Takahashi and colleagues [37] showed that BMMNCs in rats produce and release various cytoprotective factors, including vascular endothelial growth factor, platelet-derived growth factor, interleukin-1β, and insulin-like growth factor-1, some of which are significantly up-regulated by hypoxia. These paracrine factors may influence adjacent cells and exert their actions via several mechanisms, including myocardial protection and neovascularisation. Furthermore, in humans, direct injection of BMMNCs during acute ischaemia results in a direct cardioprotective effect, by abolishing the process of apoptosis and necrosis [38], which in part explains the clinical benefit seen in clinical trials. This cardioprotective mechanism appears to be dose related with the benefit only seen with injected doses that are $\geq 5 \times 10^6$.

Neo-angiogenesis in the peri-infarct zone is an integral part of the cardiac remodelling process [39]. Under normal circumstances, however, this is seldom sufficient to meet the demands of the hypertrophied myocardium, and the compensatory tissue growth required for myocardial contractility. One of the therapeutic advantages of bone marrow-derived cells is to induce therapeutic angiogenesis in ischaemic tissues, which in turn would augment oxygen supply [40-43], and help rescue cells from critical ischaemia [44]. Dowell and colleagues [45] have shown with histological examination at 2 weeks post-infarction that injection of CD34+ cells was accompanied by a significant increase in infarct zone microvascularity, cellularity and fibrosis in comparison to controls. They also showed that neoangiogenesis was increased within both the infarct zone and the peri-infarct rim in rats receiving CD34+ cells compared with saline controls [45].

Paracrine factors released by transplanted stem cells may alter the extracellular matrix, resulting in more favourable post-infarction remodelling and strengthening of the infarct scar. In animal models of MI, the injection of endothelial progenitor cells or bone marrow-derived stem cells significantly improved blood flow and cardiac function and reduced left ventricular scarring [46,47]. After an ischaemic event, the efficiency of engrafment differs between different progenitor subpopulations [48,49]. The formation of new blood vessels occurs as a result of the interaction of different types of stem cells with cardiomyocytes [46,50-53]. Neovascularisation is mediated by the physical integration of progenitor cells into new capillaries [48,54], or through a paracrine effect by releasing growth factors that promote angiogenesis

[55], depending on the cell type and the circumstances of the cardiac injury.

Route of cell administration
The three routes of stem cell delivery that have been used so far in clinical trials are through intracoronary or intramyocardial injection or peripherally through the systemic circulation. It is not yet possible on the basis of existing clinical studies to assert a 'best' mode of delivery. However, it is likely that patients' individual pathobiology as well as the aetiology of their cardiac dysfunction will ultimately dictate the route chosen among potential progenitor cell therapies. 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 chemo-attractants for neoangiogenesis. Even after infarction, however, the absolute number of progenitor cells detected in the heart is very low [40,41,56,57], but intracoronary infusion of progenitor cells may enhance local accumulation and homing compared to intravenous injection.

By contrast, the benefit of direct intramyocardial cell delivery into hibernating myocardium is that it negates the need for the uptake of progenitor cells from the circulation. Electromechanical (NOGA) mapping is essential to ensure that the cells are injected in areas of hibernating myocardium [58], as necrotic areas of myocardium and scar tissue lack the necessary cues for cells to engraft and differentiate, and cells injected in these areas die immediately [59].

Homing
While homing of haematopoietic progenitor cells to bone marrow has been widely studied [60], the mechanisms of homing of progenitor cells to areas of tissue injury remain poorly understood. Homing is a complex process involving integrins and chemokine receptors, which is greatly enhanced after myocardial ischaemia and hypoxia. It includes adhesion to and transmigration through the endothelium followed by migration and invasion of the target tissue. Homing of cells is dependent on migration out of the vessel into the surrounding myocardium; therefore, underperfused regions of the myocardium are targeted in a less efficient manner [61]. The two key factors that play an important role in homing after a MI are the release of stromal-cell-derived factor (SDF)-1 and a chromatin binding protein (HMGB1). SDF-1 regulates homing of stem cells to ischaemic tissue through integrin-dependent adhesion [62-64], and local delivery of SDF-1 can enhance progenitor cell recruitment and neovascularisation [65,66]. The release of HMGB1 may act as a danger signal and stimulate the homing of stem cells to ischaemic tissue [67].

Furthermore, endothelial progenitor cells express a number of chemokine receptors, such as CXCR2, CXCR4 and CXCL12. These chemokines play an important role in the homing and mobilisation of endothelial progenitor cells and their recruitment to the site of ischaemic injury for endothelial recovery [68-71].

Where is research in this area heading in the next few years?

The need for new therapies to treat patients with AMI has led to a swift transition from bench to bedside and a number of clinical trials showing promising potential for stem cell therapy in heart disease. The ultimate aim of this research is to develop a technique that grows new functioning heart muscle. However, many obstacles still lie ahead. One of the many remaining unanswered questions is which type of stem/progenitor cell is the best candidate for cardiac regeneration. The bone marrow is an attractive source because it is easily accessible and contains a number of stem cells, including haematopoietic and mesenchymal cells. It is likely, however, that bone marrow cells in humans work through an indirect paracrine mechanism. The safety and feasibility of bone marrow cells in AMI have been well established in clinical trials. This, therefore, supports the need for robust evidence from large double-blind randomised controlled trials to assess their effect on clinical endpoints such as mortality and symptoms.

The European Society of Cardiology established a task force to investigate the role of stem cells in cardiac repair and published its consensus in a 2006 report [72]. The future focus in stem cell therapy should be to provide a better understanding of the mechanism of functional improvements observed and the development of safe and effective cell tracking modalities. These areas of research would aid the identification of the best cell candidate for therapeutic use as well as better understanding of myocardial homing and cell survival post-transplantation. It is important to note, however, that the clinical experience has provided a lot of valuable information regarding the approaches to cell therapy in humans, which will of course provide a platform for future trials in this field.

One of the challenges in the future is improving the durability and survival of stem cells in the adverse environment they are engrafted into. One of the properties of stem cells is stress resistance [73], although several studies have shown that most stem cells die within a few weeks of delivery into the myocardium [34,74-76]. This is probably due to the lack of nutrients and oxygen within the ischaemic environment. Furthermore, heart failure [77], atherosclerosis [78,79] and advanced age [80,81] correlate inversely with the number and function of circulating endothelial progenitor cells. Allogenic cells from young and healthy donors may represent a good solution, but cell rejection requiring immunosuppressive therapies would pose a new problem. There is some evidence that statins improve the survival of the circulating endothelial progenitor cells [82,83]. Furthermore, higher doses of statin therapy are associated with a greater increase in circulating $CD34^+$ and $CXCR4^+$ from the bone marrow, resulting in an increase in coronary flow reserve at 8 months [84]. Future trials are on the horizon assessing the role of statin therapy on enhancing the number of endothelial cells in patients with coronary artery disease (Clinicaltrials.gov CT01096875). Endothelial progenitor cells are a subset of haematopoietic cells that have an important role to play in ischaemia by promoting angiogenesis, preventing cardiomyocyte apoptosis and reducing adverse remodelling. It may be that future potential remedies, such as statins, that enhance the function of endothelial progenitor cells may play an important role in improving stem cell survival and function. One of the ways of improving cell survival may be achieved by using viral vectors encoding multiple cytoprotective genes that act on different cell death and apoptotic pathways, or by preconditioning the stem cells with cytokines that result in improved cell engraftment.

Another important issue is the timing of cell administration post-MI. Although animal studies have supported early administration of stem cells post-infarction, in humans the benefits of this therapy were greater when administered >4 days after reperfusion (based on available evidence). Furthermore, given the seemingly small improvements that these trials have shown, the cost-effectiveness of cell therapy will also need to be addressed.

Two ongoing randomised controlled trials (TIME and late TIME studies) may help us understand whether the timing of cell administration plays an important role. The TIME study (Clinicaltrials.gov NCT00684021) is a trial designed to assess the effect of timing (3 versus 7 days) of BMMNC administration versus placebo in patients with acute MI. The LATE TIME study (Clinicaltrials.gov NCT00684060) will assess the effect of BMMNC administration 2 to 3 weeks after a MI.

Future cells

Animal and human studies have clearly shown that stem cell engraftment into the myocardium is associated with improvement in cardiac function; however, the quest for the optimal population of cells remains a challenge [85,86]. Embryonic stem cells are able to transform into cardiomyocytes and can replicate indefinitely, although ethical issues - their potential to form teratomas and the need for immunosuppressive therapy - have hindered their use in clinical trials. Furthermore, one of the major limitations of adult stem cells, including skeletal myoblasts and bone marrow-derived stem cells, is their limited ability to cross their lineage boundaries.

Fat tissue-derived multipotent stem cells [87], multi-potential cells from bone marrow or skeletal muscle [88,89], somatic stem cells from placental cord blood [90], and cardiac-resident progenitor cells [32,91] all show promising pre-clinical and some clinical applications.

Ultimately, cells that more closely resemble embryonic stem cells in their regenerative potential without the ethical issues provide an important future direction. A cell type that comes close, and is on the horizon of being tested for potential clinical application, is the inducible pluripotent stem cell (iPSC). iPSCs can be generated from adult human somatic cells by retroviral transduction [92], have similar differentiation potential and may provide an alternative to pluripotent embryonic stem cells.

The future of bone marrow stem cells

For the time being, it is important to establish whether the simple unfractionated bone marrow cell approach has clinical benefit, given the large number of studies that have been performed using this cell type without providing a clear answer. Meta-analysis suggests a positive effect on surrogate cardiac end-points in studies using BMMNCs to treat AMI. There is now a need to perform a large scale clinical trial using clinical hard end-points such as mortality to establish whether the positive effects seen on surrogate end-points can indeed translate to meaningful clinical benefits.

Abbreviations

AMI, acute myocardial infarction; ASTAMI, Autologous Stem-Cell Transplantation in Acute Myocardial Infarction; BMMNC, bone marrow-derived mononuclear cell; BOOST, Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration; EF, ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; REPAIR-AMI, Intracoronary bone marrow derived progenitor cells in acute infarction; SDF, stromal-cell-derived factor.

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