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Stem cell therapies for ischemic heart disease: clinical trial outcomes and futures

Abstract

Ischemic heart disease carries high morbidity and mortality despite modern pharmaceutical treatment and revascularization procedures. Biologic stem cell therapy offers the potential to revolutionize clinical outcomes for ischemic heart disease by reducing scarring and improving cardiac function. Several small randomized clinical trials have been done utilizing various methodologies, different types of stem cells and doses, and measuring different clinical outcomes. The findings of these individual studies, as well as larger meta-analyses, have been inconsistent likely due to the significant heterogeneity within the methods used. In this review, we provide a more structured approach by comparing the recent studies by type of disease, stem cells, dose, delivery method, and outcome in an effort to draw attention to the similarities and differences in these studies and the need for a standardized approach in larger trials. We show that out of all the current stem cell therapies that have been tried, Adult stem cells, primarily mesenchymal stem cells are currently the most promising for post-myocardial infarction and heart failure while granulocyte colony-stimulating factor and bone marrow mononuclear treatment show efficacy in treating ischemic cardiomyopathy. Lastly, we discuss the potential future directions of stem cell therapy for clinical application in ischemic heart disease.

Keywords: mesenchymal stem cells, granulocyte colony-stimulating factor, human germline pluripotent stem cells, ischemic cardiomyopathy, ischemic heart disease

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Introduction

Ischemic heart disease is often attributed to heart damage from acute myocardial infarction or ischemic cardiomyopathy. It is a leading cause of heart failure and often associated with high morbidity and mortality, accounting for one in nine deaths in the United States.[1,2] Furthermore, among those admitted to the hospital with heart failure, medical costs are high and survival rates are low, with only ten percent expected to survive 10 years.[1] Despite many advances in pharmacologic therapies and revascularization procedures for cardiovascular disease, the main treatment options for heart failure still include the use of a left ventricular assist device (LVAD) or a heart transplant, which is why there is interest in alternative stem cell therapies (with their potential to regenerate cardiac tissue) particularly for patients who have no further treatment options.[1,2]

The exact mechanisms for the clinical benefit seen with stem cell treatment on cardiac disease are not fully understood. Some proposed ideas are that the stem cells can promote immunomodulatory effects, reduce myocardial apoptosis and fibrosis, promote angiogenesis, and exert paracrine modulation.[3] Different stem cell populations, like mesenchymal stem cells (MSCs) and bone marrow-derived mononuclear cells (BM-MNCs), are two subsets that have been commonly used in the clinical trials that are analyzed in this review.

MSCs are considered multipotent stem cells that can be found in different tissues including but not limited to bone, muscle, fat, and umbilical cords.[2] Since these cells are considered multipotent they do not contribute to teratoma formation. There are some limitations associated with MSCs, one being the culture and growth process which can be time-consuming.[2]

BM-MNC are stem cells derived from bone marrow with single nuclei. They are also considered multipotent. They contain hematopoietic cell populations as well as nonhematopoietic cell populations such as erythroid progenitor cells and mesenchymal cells mentioned above. Given their abundance in the bone marrow and ease of isolation, expansion and purification, they are the most researched stem cell source.[2]

While several studies have been done to assess both the safety and efficacy of stem cell treatment, the findings have been mixed with some highly cited studies showing improvements in left ventricular ejection fraction (LVEF)[3,4] and others showing no efficacy for ischemic heart disease.[5,6] It is difficult to directly compare the studies because of the use of different types of stem cell treatments, doses of stem cells, mechanisms of delivery, patient populations, and measurable outcomes. As a result, this review has focused on looking at these key aspects of the study methods and outcomes and has organized the data across the three ischemic cardiovascular diseases of interest: post-acute myocardial infarction, ischemic cardiomyopathy, and heart failure.

Acute Myocardial Infarction (AMI)

A variety of different types of stem cell therapies, including granulocyte colony-stimulating factor (G-CSF), BM-MNCs, $CD133^+$ bone marrow cells, and MSCs, have been investigated in clinical trials to treat patients who experienced a recent myocardial infarction. However, many of these treatments have not yet yielded positive results. In this section, we analyze 13 selected clinical trials (summarized in Table 1) that examined the clinical outcomes, primarily LVEF, of post-AMI patients treated with various stem cell therapies. Trials involving the use of G-CSF treatment did not yield any statistically significant changes in LVEF.[5,7] Studies with BM-MNCs and $CD133^+$ bone marrow cells had mixed results with some promising early trials, but later follow-up trials showed no significant improvements.[6,8-10] Lastly, MSC therapy has been the most successful treatment tried so far, with several encouraging studies.[4,11]

G-CSF treatment has been shown to have no significant effect on clinical outcomes for acute MI patients. G-CSF facilitates the

mobilization of stem cells from bone marrow to the peripheral bloodstream and was hypothesized to improve cardiac function by traveling to ischemic areas of the heart and differentiating into specialized cardiac cells.[7] In the REVIVAL-2 Trial, patients in the treatment group received a 10 μg/kg daily subcutaneous dose of G-CSF after successful reperfusion via percutaneous coronary intervention (PCI). Infarct size decreased and LVEF increased for the placebo and treatment groups six months post-MI, but there were no significant differences between the groups.[7] The MAGIC Cell 1 Trial examined whether there were any differences in outcomes when treating patients with G-CSF to stimulate stem cell mobilization or providing intracoronary infusions with mobilized stem cells. At two years follow-up, G-CSF treatment alone did not improve LVEF or cardiac remodeling. While the intracoronary infusion and control groups showed improvements, the differences between the groups were not statistically significant.[5] The study also evaluated the safety of G-CSF therapy and found that it did not significantly increase the risk of major adverse cardiac events (MACE), such as deaths, significant arrhythmias, and recurrent MIs. However, there was a non-significant increase in binary restenosis in patients who received G-CSF treatment.[5]

Table 1 Clinical trials for stem cell therapies in patients post-myocardial infarction

Name of trial and authors	Study design	Eligibility criteria	N	Type of stem cell treatment/dose	Clinical efficacy outcomes
REVIVAL-2 Trial[7]	Double-blind randomized control trial	Successful reperfusion	114	G-CSF treatment for stem cell mobilization, 10 μg/kg daily	Changes in infarct size at 4-6 months, measured by technetium-99-labeled single-photon-emission CT LVEF at 4-6 months, measured by MRI No significant improvement in LVEF
MAGIC Cell 1 Trial[5]	Phase II randomized control trial	-	30	G-CSF treatment for stem cell mobilization vs. infusion of mobilized stem cells with G-CSF	LVEF at 1 and 2 years follow-up, measured by SPECT No significant improvement in LVEF
MiHeart/ AMI Study[6]	Multicenter, double-blind randomized control trial	LVEF < 50% Successful reperfusion	121	Bone marrow- derived mononuclear cells	LVEF at 6 months, measured by MRI No significant improvement in LVEF
TIME Trial[9]	Randomized double-blind placebo-controlled trial	Anterior STEMI treated with successful primary PCI, LVEF ≤ 45%	85	Bone marrow mononuclear cells (150 million) vs. placebo	LVEF, regional function, infarct size, LV volumes, and microvascular obstruction after 2 years by cardiac magnetic resonance imaging (cMRI) No significant improvement in LVEF
Swiss-AMI Trial[12]	Randomized open-labeled control trial	Acute STEMI with successful PCI and LVEF ≤ 45%	200	Intracoronary bone marrow mononuclear cell infusion 5-7 days post-PCI vs. 3-4 weeks post-PCI vs. standard of care	LVEF, LV volumes, scar size, and N-terminal pro-brain natriuretic peptide levels after 4 months and 12 months by cardiac magnetic resonance imaging No significant improvement in LVEF
Laguna et al.,[13]	Randomized controlled trial	Non-revascularized transmural expired AMI, LVEF ≤ 50%	20	Bone marrow mononuclear stem cell grafting by direct intramyocardial injection (10 million cells) plus CABG vs. CABG only	LVEF, global and regional wall motion after 9 months No significant improvement in LVEF
BOOST-2 Trial[10]	Randomized controlled, placebo-controlled double-blind trial	STEMI with successful PCI and hypokinesia/ akinesia of > ⅔ of LV	153	Intracoronary infusion of high-dose autologous nucleated bone marrow cells (BMCs), low-dose BMCs, irradiated high-dose BMCs, irradiated low-dose BMCs or placebo; High-dose was about 20 x 108 cells and low-dose was about 7 x 108 cells);	LVEF 6 months after by MRI

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Table Continued...

Name of trial and authors	Study design	Eligibility criteria	N	Type of stem cell treatment/dose	Clinical efficacy outcomes
				Note: all patients underwent bone marrow harvest	No significant improvement in LVEF
Yang et al.,[14]	Phase II, double-blind randomized control trial	STEMI in left ventricular anterior wall, 2-4 wks LVEF < 45%	100	Autologous bone marrow mononuclear cells (with atorvastatin)	LVEF at 1 year, measured by MRI
					LVEF significantly improved
Stamm et al.,[8]	Randomized controlled trial	History of MI (>14 days post-MI) and indication for CABG	40	CD133(+) cell treatment plus CABG vs CABG only	LVEF after 6 months
					LVEF significantly improved
Cardio133 Trial[15]	Randomized double-blinded controlled trial	CABG indication plus LVEF <35%	60	CD133(+) cell treatment plus CABG vs CABG only	LVEF after 6 months by cardiac MRI
					No significant improvement in LVEF
PERFECT Phase III Clinical Trial[16]	Randomized multicenter, placebo-controlled double-blinded phase III study	Coronary artery disease post-MI with CABG surgery indication and reduced LVEF (25-50%)	82	Intramyocardial injection of CD133+ bone marrow stem cells (0.5-5 x 106)	LVEF after 180 days
					No significant improvement in LVEF
SEED-MSC Trial[4]	Multicenter randomized control trial	ST-segment elevation > 1 mm in two consecutive leads, > 2 mm in precordial leads	58	Autologous bone marrow-derived mesenchymal stem cells	Global LVEF at 6 months, measured by SPECT
		Successful reperfusion			LVEF significantly improved
Kim et al.,[11]	Randomized control trial	ST-segment elevation > 1 mm in two consecutive leads, > 2 mm in precordial leads EF < 40%	26	Mesenchymal stem cells	LVEF at 4 and 12 months, measured by echocardiography
		Successful reperfusion			LVEF significantly improved

The use of BM-MNCs has yielded conflicting results for treatment of patients post-acute MI. The MiHeart Study measured LVEF in patients via MRI, six months after treatment, and found that the mean LVEF was similar in the treatment and placebo groups. Furthermore, there were no differences in left ventricular remodeling and infarct size between the groups.[6] In the TIME Trial, intracoronary infusion with 150 million BM-MNCs did not improve LVEF after two years.[9] There was no difference in regional LV function between the placebo group and the BM-MNC treatment group, and both infarct size and LV mass decreased in both groups over time.[9] One potential confounding factor in the study was that cardiac magnetic resonance imaging (cMRI) was used in evaluating LV function. cMRI cannot be used in patients who receive an implantable cardioverter-defibrillator (ICD) or pacemaker, so those patients were excluded from the rest of the study potentially skewing results.[9] The SWISS-AMI Trial also found that there were no significant differences in LVEF after twelve months, independent of whether patients received autologous BM-MNCs at five to seven days or three to four weeks after acute MI.[12] Similar to the TIME Trial, the SWISS-AMI Trial utilized cMRI to analyze LV function and experienced a high patient dropout rate, although adjustments for missing data were made in the analyses.[12] Interestingly, the levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), which is released from the heart under increased pressures and can be used to measure heart failure, nearly normalized in the group treated with BM-MNCs from four to twelve months after treatment. However, the group treated with placebo did not have a decrease to normal levels in NT-proBNP after twelve months.[12] Another small study with 20 patients looked at the effect of BM-MNC treatment with a dose of 10 million cells via direct intramyocardial injection in addition to coronary artery bypass graft (CABG) versus CABG only. After 9 months, no significant differences in LVEF or global and regional wall motion were seen.[13]

Lastly, although the first BOOST trial found a statistically significant increase LVEF in patients receiving nucleated bone marrow cell treatment, the subsequent BOOST-2 trial, which compared intracoronary infusion of high-dose autologous bone marrow cells (BMCs) versus low-dose BMCs, irradiated high-dose BMCs, irradiated low-dose BMCs, and placebo, did not find any significant improvements in LVEF six months after treatment.[10] The authors postulated that this may be because earlier trials such as the BOOST trial were done before PCI was the standard of care post-MI. Thus, at that time, BMC treatment may have had a greater positive effect than now, when patients typically receive PCI and achieve successful reperfusion.[10] Another potential variable is the heterogeneity of BM-MNC harvests. Older patients and patients with preexisting medical conditions, who are more likely to have ischemic heart disease, have been found to have BM-MNCs with reduced regenerative capacity compared to patients who are young and healthy.[12]

Interestingly, a recent study discovered that BM-MNC transplantation improved cardiac function by increasing LVEF after a one-year follow up in patients who also received intensive atorvastatin treatment.[14] In animal studies, atorvastatin has previously been shown to improve cardiac function (by reducing oxidative stress and ameliorating the effects of pro-inflammatory cytokines), protect endothelial cells, and exert anti-apoptotic effects.[14] Adding atorvastatin to the treatment regimen could increase LVEF by improving the

myocardial microenvironment and protecting the BM-MNCs from harsh conditions that can decrease their efficacy. The results of the study also pointed to potential cardiac repair and remodeling for patients with intensive atorvastatin and BM-MNC therapy, as there was a significant decrease in both infarct scar size and NT-proBNP levels as well as an increase in the area of viable myocardium.[14] It is important to note that the improvement in LVEF was only seen in high dose atorvastatin (80 mg/day).[14] There was no significant difference in LVEF between patients who received regular atorvastatin (20 mg/day) treatment alone or those who received regular atorvastatin treatment along with BM-MNC transplantation.[14] Despite the mixed outcomes of these trials, BM-MNC treatments were found to be relatively safe and were not observed to have any significant adverse clinical effects.

$CD133^+$ bone marrow cells have also been investigated as a potential therapy for ischemic heart disease, although there have been conflicting results. An earlier trial with 40 patients by Stamm et al.,[8] found a statistically significant increase in LVEF in patients who received both $CD133^+$ cell therapy and CABG in comparison to patients who received CABG alone. Unfortunately, in 2014 when the Cardio133 trial looked at the effect of $CD133^+$ cell therapy in addition to CABG surgery in patients who had ischemic heart disease, they found no significant improvement in LVEF for patients who received the stem cell therapy compared to patients who underwent only the CABG procedure.[15] The authors of the recent PERFECT Phase III trial, which involved the use of intramyocardial $CD133^+$ therapy in patients post-MI with reduced LVEF, did a post-hoc analysis where the patients were split into two categories: responders and non-responders based on LVEF improvement (Steinhoff et. al., 2017). They found that those whose LVEF improved by at least five percent six months after treatment had higher circulating $CD133^+$ endothelial progenitor cells and thrombocytes before undergoing treatment than the patients classified as non-responders.[16] Future trials may thus use the level of circulating $CD133^+$ progenitor cells as a criteria for selecting patients who are most likely to benefit from the $CD133^+$ bone marrow cell therapy.[16]

Importantly, several studies have shown the promising beneficial effects of MSC therapy on improving outcomes in acute MI patients. The SEED-MSC Trial found that bone-marrow derived MSC intracoronary injection improved LVEF at six months follow-up.[4] Another study similarly found that MSC intracoronary injection improved LVEF at four and twelve months follow-up.[11] The mechanism behind the increased LVEF was attributed primarily to an improvement in systolic wall motion of the infarcted area, rather than an improvement in left ventricular remodeling.[11] Both studies found that MSC injections did not increase the risk of MACE, with no serious complications.[4,11] Although MSC therapy has been promising, it is hypothesized that the beneficial effects are due to the paracrine action of the stem cells and not successful engraftment or differentiation into cardiomyocytes.[17] MSCs are thought to promote angiogenesis, have anti-inflammatory effects, and promote survival and proliferation of cardiac cells through their secretory products.[17]

Overall, a plethora of different types of stem cell therapies have been tried in clinical trials for post-MI patients. Although G-CSF, BM-MNC, and $CD133^+$ bone marrow cells seemed to be promising treatments, few studies have shown encouraging results. MSC therapy has had the most positive outcomes thus far, and more follow-up trials should be done to further elucidate their clinical benefit.

Ischemic cardiomyopathy

Cardiomyopathy is a disease of the heart muscle where the heart struggles to fill and pump blood and can be associated with abnormal heart rhythms. Ischemic cardiomyopathy (ICM) is typically caused by scarring and fibrosis from myocardial infarctions and can lead to heart failure.[1]

Three recent randomized controlled studies (listed in Table 2) have assessed the efficacy of stem cell treatments for patients with ICM and left ventricular dysfunction (or reduced LVEF).[1,18,19] Though the criteria for the study population was similar across all three studies, Choudhury et al.,[1] specifically included patients with ICM who were more sick and for whom there were no further revascularization or treatment options. Noiseux et al.,[19] specifically included patients undergoing CABG and thereby still exploring other revascularization treatment options. These slight differences in study eligibility may affect which patients would benefit more from stem cell treatment.

Table 2 Clinical trials for stem cell therapies in patients with ischemic cardiomyopathy

Name of trial and authors	Study design	Eligibility criteria	N	Type of stem cell treatment/dose	Clinical efficacy outcomes
REGENERATE-IHD[1]	Randomized placebo controlled trial	Symptomatic Ischemic cardiomyopathy (ICM) diagnosed with ischemic heart failure on medical treatment for at least 6mo. with impaired LVEF and without any further revascularization options.	90	Granulocyte colony stimulating factor (G-CSF) given prior to harvesting 50mL of autologous BMC cells which were then centrifuged. 2mL aliquot of BM-MNCs was delivered either by intramyocardial injection or intracoronary injection	Improvement in LVEF at 1yr was assessed by cardiac MRI. Study findings show that G-CSF combined with autologous bone marrow derived cells (BMC) delivered via intramyocardial injection had improvement in LVEF of 4.99% (p=0.04), a reduction in NYHA class at 1year, and reduction in NT-proBNP at 6mo
					LVEF significantly improved
IMPACT-CABG[19]	Multicenter phase II randomized placebo controlled trial	Chronic ICM undergoing coronary artery bypass grafting (CABG)	40	Up to 10million CD133+, CD34+, CD45+ cells harvested from autologous BMCs and injected intramyocardially during CABG	Stem cell delivery during CAGB was found to be safe and feasible with no major adverse cardiac events.
					Clinical follow up of LVEF with MRI after 6mo showed improvement in ejection fraction in all patients.
					LVEF improved, but data is not statistically significant

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Table Continued...

Name of trial and authors	Study design	Eligibility criteria	N	Type of stem cell treatment/dose	Clinical efficacy outcomes
TRIDENT[18]	Phase II Randomized study (no placebo control),	Patients with chronic ischemic left ventricular dysfunction following myocardial infarction	30	Two different doses given of either 20million or 100 million allogeneic bone marrow derived human mesenchymal stem cells via transendocardial injection	Both cell doses (20million and 100million) reduce scar size -6.4g and -6.1g respectively (p<0.001) 100 million cell dose increased LVEF by 3.7U (p=0.04) 20million cell dose saw 0.32 log pg/mL increase in proBNP (p=0.04) LVEF significantly improved

In addition, each study has used different outcome measures to assess clinical efficacy. Choudhury et al.,[1] evaluated 90 patients with ischemic cardiomyopathy and compared whether G-CSF on its own or combined with intracoronary or intramyocardial injection of autologous BM-MNCs would show any additional improvement in LVEF at twelve months compared to baseline. They found that patients who received intramyocardial injections of BM-MNCs after being dosed with G-CSF had a significant improvement of 4.99% in LVEF after one year (p=0.038).[1]

Noiseux et al.,[19] evaluated 40 patients and focused primarily on using specific autologous BMCs including CD133+, CD34+, and CD45+, which are multipotent stem progenitor cells involved in hematopoiesis and vasculogenesis. They were delivered via intramyocardial injection into the revascularized tissue after coronary artery bypass grafting. They primarily evaluated the safety of this same day procedure and found that there were no serious adverse events. They also evaluated the changes in LVEF and saw an improvement in all patients, regardless of whether they received stem cells or placebo.[19] The study was not powered to detect a difference in the change in LVEF from baseline or between groups, but it demonstrated that LVEF is an important clinically objective measure.[19]

Florea et al.,[18] evaluated 30 patients and assessed the difference in scar size between patients receiving either 20 million or 100 million allogeneic BMC stem cells. While scar size was significantly reduced in both groups, they also found that higher doses of stem cells were associated with a significant improvement in LVEF (p=0.04).

Choudhury et al.[1], Noiseux et al.,[19] and Florea et al.,[18] used changes in LVEF as an outcome measure because ischemic cardiomyopathy typically presents with impairment of left ventricular systolic function due to ventricular remodeling and loss of myocardial tissue. As a result, an improvement in LVEF would indicate that the stem cell treatment has helped with the regeneration of myocardial tissue.

Differences in outcome measures are important to evaluate when comparing studies, but differences in the types of stem cells used may actually be more important to consider. All three studies noted in Table II used BMCs, and one study also used human MSCs.[1,18,19] Studies using BMCs showed more promising results for improving LVEF in patients with ICM.[1,18,19]

There was little variability between the methods of stem cell delivery. Both Choudhury et al.,[1] and Noiseux et al.,[19] delivered the treatment dose of stem cells with an intramyocardial injection, while Florea et al.,[18] delivered the dose of stem cells with a transendocardial injection. Both of these methods can be categorized together since they deliver the stem cells directly to the myocardium by different routes.[20] The intramyocardial approach is typically more invasive involving surgery and the cells are injected from the epicardium of the left ventricle; however, studies have shown that this can result in a higher cell count within the myocardium.[20] The transendocardial injection is less invasive and involves the use of a percutaneous catheter to inject cells into the myocardium.[20] Choudhury et al.,[1] also had one study arm that delivered the stem cell biologics through the intracoronary route, which involves injecting cells into a coronary vessel; however, this method did not have any significant clinical outcome.[1]

There was a lot of variability in the dose of the biologic stem cells therapy used in each study ranging from 10 to 100 million cells. While some studies have indicated that there is an inverse relationship between the total cells delivered and the clinical outcomes,[21] other studies have shown a direct dose-dependent response where those who received the highest dose of cells had the most substantial clinical improvement.[18,22] The differences in the doses of biologics, along with the different outcomes measured in these studies can make comparison of the study results much more challenging. Florea et al.,[18] specifically designed the study to assess the impact of treatment dose, though they did not have a placebo control group for comparison. Instead, Florea et al.,[18] compared 15 patients who were given 20 million allogeneic BMC derived MSC with 15 patients who were given a larger dose of 100 million stem cells. They found that both doses reduced scar size (p<0.001) while only the larger dose significantly increased the ejection fraction (p=0.04).[18] The results of this study seem to suggest that higher doses of stem cells may have a direct relationship with improved treatment efficacy.

In addition to the differences in the number of cells used in treatment, there are substantial differences and inconsistencies in how the cells were measured and evaluated within groups for analysis. Choudhury et al.,[1] did not list a total cell count delivered to each patient, but instead took a measured amount of combined fluid and cells, harvesting a 50mL aliquot of bone marrow and ultimately delivering a total volume of 2mL of BMC stem cells to the affected areas of the myocardium. The different doses, different measurements, and different methods for analyzing studies without consistent attention to the dose pose a significant limitation in understanding whether there is clinical efficacy in stem cell treatment and serve as a limitation for any future meta-analysis of this research.

Taken together, there are limitations of what we can compare between the studies when there are significant differences in dose and type of stem cell. However, we can also see some commonalities emerging between the studies which should serve as a standard for any larger trials. Each study used BMCs, and Choudhury et al.,[1] found that BMCs had an improvement in LVEF of 4.99% (p=0.04) and a reduction in NYHA class at the 12 month follow up period.[1] In a post hoc analysis, Ramireddy et al.,[23] used both BMCs and MSCs found that patients who received MSCs showed signs of improvement in ventricular arrhythmias, though the results were not significant.[23]

This indicates that different types of stem cells may offer different potential clinical benefits. In a comparison of stem cell dose, Florea et al.,[18] found that the larger dose of stem cells was associated with an increased ejection fraction and that at any dose there is a reduction in scar size and improvement in tissue remodeling.[18] While the study size was small, the findings were significant and indicate that larger studies should be done to carefully account for differences in clinical outcomes associated with differences in both type of stem cell and dose. Lastly, stem cell delivery through intramyocardial injection seemed to have improved LVEF outcomes compared with intracoronary injection as seen in Choudhury et al.[1] It is important for future studies to consider using a consistent approach to measure clinical outcomes, and enroll a larger study population with an appropriate power to detect a difference in LVEF, scar size, and antiarrhythmic properties.

Heart failure

Any patient with ischemic heart disease is at risk of developing heart failure.[2] Heart failure is a progressive disease and carries with it a poor prognosis. Despite current advances in pharmacologic therapy for slowing progression and ventricular remodeling, there has been recent research in stem cell therapy for the treatment of heart failure with hopes to see improvement in ventricular function. Still, there need to be more trials to hone in on the right dosages, routes of administration, and optimal stem cell populations, until they can become more routine clinical treatment options.[2] The goal of this section is to evaluate the literature on stem cell therapy for the treatment of heart failure with reduced ejection fraction (HFrEF) and sort through some of the criteria mentioned above as well as evaluate the clinical outcomes.

Positive results were seen in the Randomized Clinical Trial of Intravenous Infusion Umbilical Cord Mesenchymal Stem Cells on Cardiopathy (RIMECARD) Trial.[3] Umbilical cord mesenchymal stem cells (UC-MSC) were used in the treatment of patients with HFrEF. The use of umbilical cord-derived stem cells present some advantages in that umbilical cords are normally medical waste and thus have no ethical concerns associated with using them.[3] They also have less cellular aging and do not require invasive procedures to harvest outside of cesarean section delivery as compared to other adult MSCs such as bone marrow harvest.[3] In the RIMECARD trial patients in the experimental group received a single dose of 1×10^6 UC-MSCs/kg of body weight intravenous infusion of UC-MSC. Results showed statistically significant improvement in LVEF, VE/VCO_2, and quality of life based on the Kansas City Cardiomyopathy questionnaire as compared to the control group.[3]

The Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART-1) study used MSCs and aimed to assess the dose-response curve as well as left ventricular remodeling.[24] Left ventricular remodeling has been previously associated with adverse outcomes in patients with heart failure and therefore reverse remodeling can be used as a measure and target for improvement.[24] In this study, the experimental group received 0.5mL intramyocardial injections with concentrations of 57 – 60x10^6 cells/mL. The number of injections varied from either 14 or fewer injections up to 21 injections to assess the dose-dependent outcomes. Decreased benefits were seen in patients receiving greater than or equal to 20 injections and the greatest efficacy was seen with a moderate (15-19) number of injections.[24] Some theories proposed by the authors were that there may be an increased risk of myocardial damage and inflammation with an increased number of injections.[24] Primary outcomes seen in this study were that the left ventricular end systolic (LVESV) and diastolic volumes (LVEDV) decreased significantly more in the experimental versus the control group.[24] In contrast to the RIMECARD trial, there was no difference seen between the two groups in terms of LVEF. However, both groups did have an increase in ejection fraction compared to baseline.

The REPEAT study reports that two doses may be better than one in terms of intracoronary injections of BM-MNC.[25] The study assessed patients receiving either single or repeated intracoronary injections in 297 post-infarction heart failure patients. A mean number of $190 \pm 110 \times 10^6$ cells were used for the intracoronary injections. They found a statistically significant improvement in two year survival in patients receiving a second dose versus the single dose group.[25]

The cardiAMP heart failure trial is a current clinical trial studying the use of high dose BM-MNC for treatment of medically refractory and more advanced heart failure (NYHA functional class II-III failure patients with an LVEF of 20-40%).[26] The target dose is 200 million cells, similar to the REPEAT trial. The cardiAMP study was intended to expand on the results from the TAC-HFT (Transendocardial Mesenchymal Stem Cells and Mononuclear Bone Marrow Cells for Ischemic Cardiomyopathy) study which assessed the differences between MSCs and BM-MNCs clinical outcomes for patients with chronic ischemic cardiomyopathy with LV dysfunction resulting from an MI.[27] The study showed that MSCs had more promising outcomes as compared to BM-MNC or placebo in regards to reduction in infarct scar size, amount of viable tissue mass, and 6-minute walk test.[27]

While many studies mentioned above aimed at a higher dose, the POSEIDON randomized trial compared doses of 20, 100, and 200 million of autologous and allogeneic MSCs in patients with LV dysfunction.[21] The cells were delivered via 10 different transendocardial injections. The results show that allogeneic cells reduced LVEDV and the low dose (20 million) produced the greatest results with a decrease in LVEDV and an increase in EF.[21]

In summary, many trials on the use of stem cell therapy in patients with HFrEF have produced positive clinical outcomes (summarized in table 3). The TAC-HFT trial showed MSC therapy had more therapeutic benefit compared to BM-MNC.[27] Studies have evaluated a wide range of dosages with benefits seen at both high and low doses. The POSEIDON trial suggests that a lower dose may be better and the REPEAT study suggesting that multiple doses may produce better results than a single dose.[21,25]

Table 3 Clinical trials for stem cell therapies in patients with heart failure

Name of trial	Study design	Eligibility criteria	N	Type of stem cell treatment/dose	Clinical efficacy outcomes
RIMECARD Tria[3]	RCT	Chronic HFrEF with (NYHA) classification I to III and (LVEF) ≤40%	30	UC-MSCs 1×10^6 cells/kg Single dose IV	Treatment group showed significant improvement in LVEF at 3, 6, and 12 months of follow-up. At 12 months, UC-MSC–treated patients reported improvement in quality-of-life

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Table Continued...

Name of trial	Study design	Eligibility criteria	N	Type of stem cell treatment/dose	Clinical efficacy outcomes
CHART-1 study[24]	RCT	Chronic HF secondary to ischaemic heart disease, reduced LVEF <35%, and at high risk for recurrent HF-related events despite optimal medical therapy were eligible for the study	315	Range of 14 to 21 0.5 mL injections containing 57 – 60x10^6 cells/mL of bone marrow derived mesenchymal stem cells.	Treatment group showed a significant decrease in both LVEDV and LVESV more in the active arm than in controls. No change seen in LVEF or LV mass between the two groups. Best results seen in patients receiving a moderate number of injections (<20).
REPEAT trial[25]	Cohort	Chronic HF symptoms NYHA ≥II, had a previous, successfully revascularized myocardial infarction at least 3 months before BM-MNC administration and had a well-demarcated region of left ventricular dysfunction	297	1x vs 2x intracoronary injections of 190 +/- 110 × 10^6 BM-MNC	Statistically significant improvement in 2 year mortality in 2x dose vs 1x dose groups
TAC-HFT trial[27]	RCT	Ischemic cardiomyopathy with LV dysfunction resulting from chronic MI, and had LVEF of less than 50%	65	MSC vs BM-MNC vs placebo	Greatest results seen with MSCs, then BM-MNC followed by placebo. MSC showed reduction in scar size, increase in viable tissue mass and improvement in and functional 6 minute walk test.
POSEIDON trial[21]	Randomized comparison	Chronic ischemic LV dysfunction secondary to MI, LV ejection fraction (EF) of less than 50%	30	20, 100, or 200 million allogenic or autologous MSCs	Greatest results seen with allogeneic cells and 20 million dose, showing decrease in LVEDV and increase in EF

Conclusion

MSC therapy was shown to yield the most promising benefits in treating acute MI and heart failure by improving cardiac function. For instance, for heart failure, the TAC-HFT trial showed that MSC therapy was more effective in improving clinical outcomes than BM-MNC therapy.[26] On the other hand, for ischemic cardiomyopathy, intramyocardial BM-MNCs improved LVEF in the REGENERATE-IHD Trial.[1] However, for acute MI, BM-MNC therapy was generally ineffective and only improved LVEF when augmented with intensive atorvastatin.[14] While G-CSF treatment did not show any benefits in acute MI, it increased LVEF when given with autologous BM derived cells to patients with ischemic cardiomyopathy.[1] In general, all the studies found that stem cell therapy was generally safe and resulted in very few adverse effects.[18,19]

Because there was wide study heterogeneity in both methodology and outcome measures, it was challenging to directly compare the clinical outcomes from all the studies. For example, many studies cited that one major limitation was the unclear research surrounding the optimal time for stem cell transplantation. As a result, there was a large variety of time points among studies for when the stem cell therapy was administered. Additional differences in study methodologies include the specific stem cell dosages, lengths of the follow-up periods, and different imaging modalities used to measure clinical outcomes. Another limitation that many studies discussed was the small number of patients employed in clinical trials. Out of the studies analyzed in this review, only one study had more than 300 patients enrolled. More clinical trials with a larger sample size would be needed to validate these preliminary findings.

Future directions include further elucidating the mechanisms of action underlying the different stem cell therapies and analyzing why bone marrow derived stem cells seem to be only beneficial in specific cases of heart disease such as ischemic cardiomyopathy, while MSC therapy seems to generally be more effective in patients post-MI and in patients with heart failure.[4,11,27] The benefits of MSC therapy are thought to be due to the paracrine action of the cells rather than due to successful cell engraftment or differentiation into cardiac cells.[17] Spermatogonial stem cells derived from adult human testes are an example of human germline pluripotent stem cells (hgPSCs), which have been shown to be able to be induced with appropriate growth factors to convert back to embryonic stem-like cells, which can then differentiate into all three germ layers and organ lineages.[6] Golestaneh et al.,[28] found that these hgPSCs could differentiate into mesodermal cardiac cells and confirmed this with the presence of transcription factors *GATA4, NKX2.5*, and *MEF2C*.[28] Recent advances in research have shown that these human germline pluripotent stem cells (hgPSCs) can be induced quickly to increase the growth rate of the cells by using a novel cell expansion culture for hgPSCs described by Mahapatra et al.[29] Importantly, once differentiated these hgPSC cells were found to consistently express cardiac genes and cardiac promoting paracrine factors such as VEGF, IGF-1, TGFb, and CTGF, which are cardiac protective and which can integrate into cardiac tissue in vivo.[29] They also showed that once differentiated, the hgPSC cells lose their pluripotency and do not express the genes that have been associated with teratoma formation, making them safe for clinical use.[29] Thus, these paracrine factor cardiac inducing colonies (CiCs) derived from hgPSCs may play a significant role in facilitating myocardial repair, for they have been shown to secrete paracrine factors at physiologic concentrations, which suppress fibroblast activation and excessive collagen deposition after myocardial infarction; induce cardiomyocyte migration and proliferation into the myocardial wound; and modulate matrix turnover and proinflammation.[30] In this way, recent advancements in paracrine factor stem cell research using hgPSCs has opened new possibilities for stem cell therapy in ischemic heart disease.

Future research is now moving towards investigating "cell-free" therapy where the secretomes (secreted bioproducts of MSCs) and exosomes from MSCs are packaged and directly delivered to the desired site of action by conjugation to substances such cardiac homing peptides or cell-mimicking nanoparticles.[17] Acellular therapy would potentially be used to help repair the heart and slow the progression of ischemic disease, and it poses much less risk of triggering arrhythmias or tumorigenesis.[17] Lastly, induced pluripotent stem cells (iPSCs) and human embryonic stem cells (hESCs) are still being actively investigated for their potential use in directly regenerating heart muscle and tissue in patients with ischemic heart disease.[17,29-31]

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Although iPSCs and hESCs have significant regenerative capacity and are able to differentiate into cardiomyocytes, there have not yet been many clinical trials in humans because there are still significant safety concerns due to the potential for immune rejection, risk of arrhythmias, and tumor formation.[17,31] However, one recent clinical trial involved six patients who received hESC-derived cardiovascular progenitors in a fibrin patch and found no substantial safety issues as no tumors or arrhythmias were detected in follow-up.[31] Thus, future work in stem cell therapy for ischemic heart disease will potentially also involve larger scale clinical trials testing iPSCs and hESCs, which may have a more robust effect in improving heart function.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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