Avens Publishing Group
J Cardiobiol
January 2015 Vol.:3, Issue:1

Open Access Review Article

Journal of
Cardiobiology

Stem Cell Therapy and the Heart: A Contemporary Review of the Literature

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Submission: 04 November, 2014
Accepted: 08 December, 2014
Published: 13 December, 2014

Reviewed & Approved by: Dr. Aleksandar Jovanović, Professor of Experimental Medicine, University of Dundee, UK

Abstract

Cardiovascular disease continues to bear a significant and increasing burden on global healthcare resources. Despite significant advances in medical and interventional therapies, cardiovascular disease remains the major cause of death worldwide. Beyond this, chronic congestive heart failure (CHF) affects more than 5 million Americans, only half of whom will survive the next five years. These outcomes data have spawned aggressive research efforts searching for novel therapies and treatments of both ischemic heart disease and CHF. Numerous preclinical studies over the past decade have demonstrated the benefit of stem cell therapies with respect to improvement in cardiac function. More recently, research efforts have shifted towards clinical randomized trials examining the role of stem cell therapy in a variety of cardiac conditions. This review focuses on the current status of cardiac cell based therapy while examining the most recent randomized trials including both ischemic and nonischemic cardiomyopathies with an emphasis on current and future application of these novel therapies. Despite ongoing advancements, a variety of obstacles exists and must be addressed prior to widespread clinical implementation of cell-based therapies for the treatment of cardiovascular diseases.

Introduction

The mechanisms and pathogenesis of heart failure are complex. In the setting of coronary heart disease, the presence of scar tissue coupled with the loss of functional myocytes capable of appropriate contraction and relaxation of the ventricle contributes significantly to development of ischemic cardiomyopathy. Acute myocardial infarction results in the loss of approximately 1 billion cardiomyocytes within the left ventricle during the first few hours following the onset of ischemia [1]. Historically, therapy for treatment of such cardiomyopathies has focused on strategies to limit further scar formation and tissue remodeling while promoting the functional capacity of viable myocardium [2]. Traditional therapies have provided a modest improvement in cardiovascular morbidity and mortality; yet, cardiovascular disease continues to account for 30% of global mortality and remains the single most contributory cause of death worldwide [3]. In addition, there are approximately 5.7 million individuals in the U.S. alone living with CHF, of whom only half will survive the next 5 years. CHF remains responsible for 55,000 deaths and an estimated $39 billion USD in healthcare expenditure annually, both of these indices expected to increase exponentially over the next several decades [3,4]. While ventricular assist devices and biventricular pacemakers can improve symptoms and longevity in patients with CHF, they are expensive and associated with significant risks and complications. Cardiac transplant remains a limited resource for a very narrow patient population.

Given the impact of CHF on the healthcare system, significant interest surrounds the development of novel therapies that may offer incremental benefit for ischemic heart disease and chronic heart failure. The therapeutic potential of stem cells for cardiac regeneration has become an area of intense focus for nearly a decade. Cardiomyocytes, once considered terminally differentiated, have recently been shown capable of limited repair. However, endogenous cardiomyocytes turn over very slowly and cannot efficiently replace damaged myocardium following an ischemic insult [5]. Transplantation of exogenous stem cells into the heart offers the potential to increase the number of cardiomyocytes that are electromechanically coupled and appropriately perfused by newly formed blood vessels [6]. Studies performed to date demonstrate scar size reduction and improved contractility in patients with ischemic cardiomyopathy treated with stem cells with ongoing randomized control trials currently in progress [7].

Cell Sources and Clinical Implications

Stem cells are defined as having the capacity to self-renew and to differentiate into specialized cell lines including cardiomyocytes. Numerous human cell populations have been studied experimentally, including induced pluripotent cells, bone marrow derived mononuclear cells, mesenchymal stem cells, mobilized CD34+ cells and more recently, cardiac derived c-kit+ stem cells. Many of these lineages show promise in early cardiac stem cell trials in humans [8].

Embryonic stem cells and induced pluripotent stem cells

Embryonic stem cells possess the innate characteristic of pluripotency, the ability to differentiate into all three germ layers while retaining the property of self-renewal or infinite expansion. In animal models, the use of embryonic stem cells in experimentally induced myocardial infarction and nonischemic cardiomyopathies has demonstrated significant improvement in cardiac function and cellular structure with preservation of electrical integration [9,10]. However, their use in the clinical realm has been largely limited not only by ethical concerns related to cell harvesting from early embryonic blastocytes, but also by potential immunologic reactions and the teratogenic potential of infinitely self-renewing cells [6].

Artificially produced induced pluripotent stem (IPS) cells possess many of the beneficial properties of embryonic stem cells and have been refined by reprogramming protocols with the use of microRNAs or recombinant proteins to facilitate differentiation directed toward

ISSN: 2332-3671

cardiomyocytes. Induced pluripotent stem cells, however, share the potentially teratogenic properties of embryonic stems cells, limiting their current clinical application [11].

Skeletal myoblasts

Menasche et al. first described the use of stem cells for cardiac repair in 2001 using skeletal myoblasts in a patient with ischemic cardiomyopathy, who showed significant improvement in LV function and viability at 5 month follow up [12]. These findings spawned a Phase I clinical investigation in which patients received skeletal myoblasts via epicardial transplantation at the time of coronary artery bypass grafting [12]. Their results demonstrated improved left ventricular ejection fraction (LVEF), although concern was raised regarding a subset of patients who developed ventricular arrhythmias. Subsequently, a Phase II investigation (MAGIC trial) prospectively enrolled patients who were randomized to receive either skeletal myoblast therapy or standard medical therapy alone. This trial demonstrated no significant change in cardiac function as assessed by left ventricular ejection fraction between the groups. MAGIC was terminated early owing to an observed increased in the incidence of ventricular arrhythmias in the group receiving skeletal myoblasts [13]. Subsequent studies demonstrated the inability of skeletal myocytes to express key proteins essential for appropriate electrical conduction within the myocardium, thus compromising their utility as a clinical cardiac cell therapy [2].

Bone marrow derived cells

The earliest and most noTable clinical trial involving the use of stem cells from bone marrow for the treatment of post-infarction left ventricular dysfunction was conducted by Strauer et al. in 2002 [14]. Ten patients were enrolled and underwent intracoronary infusion of bone marrow-derived mononuclear cells (a mixed cell population) into the infarct related artery at 5 days following an ischemic event. Three month follow up found significant improvement in stroke volume index, left ventricular end systolic volume and myocardial perfusion with no difference in adverse outcome as compared to the control group [14]. Several additional randomized clinical trials followed, including TOPCARE-AMI that demonstrated an improvement in ejection fraction (51.6±9.6% to 60.1±8.6% [p=0.003]) at 4 month follow up in those enrolled to receive either circulating progenitor cells or bone marrow-derived progenitor cells [15]. The BOOST trial, also a randomized controlled study, enrolled 60 patients to receive either bone marrow-derived stem cells or standard medical therapy. The stem cell treated group demonstrated a 6.7% absolute improvement in LVEF compared to 0.7% in the control group at 6 month follow up which was also maintained at 18 months [16]. The randomized, placebo controlled REPAIR-AMI trial enrolled 200 patients to evaluate the efficacy of intracoronary delivery of bone marrow progenitor cells compared to placebo in patients with acute ST elevation myocardial infarction after successful percutaneous coronary intervention. At 4 month follow up, patients receiving treatment with progenitor cells had an improvement in LVEF compared to placebo (+5.5 vs +3.0%, absolute difference +2.5%) as well as a statistically significant reduction in adverse clinical events at 1 year follow up [17].

While negative and equivocal randomized studies such as the LateTIME [18] and ASTAMI [19] trials add controversy to the use of bone marrow-derived stem cell therapy for heart disease, combined data and analysis of cohort studies and randomized clinical trials has, overall, demonstrated a favorable efficacy and safety profile. This success has prompted the first Phase III clinical trial, BAMI, currently enrolling a projected 3000 patients with acute ST elevation myocardial infarction and reduced EF ≤45%. Patients will be randomized to bone marrow- derived stem cell therapy via intracoronary infusion versus standard medical therapy after successful percutaneous reperfusion with the primary outcome of time from randomization to death (NCT01569178). Results of this study will no doubt have substantial bearing upon the future application of bone marrow-derived stem cell therapy for heart disease.

Bone marrow-derived mesenchymal stem cells are a particular subpopulation of bone marrow cells capable of differentiation into cartilage, bone or adipose tissue, and their differentiation into cardiomyocyte-like cells has also been exhibited [2]. Recent studies suggest these cells also demonstrate a paracrine function involving secretion of growth factors influencing cell-cell interactions as well as prevention of anti-donor T cell responses contributing to an immune-privileged state, both of which may enhance cellular repair mechanisms [20]. Chen et al. treated 69 patients with acute infarction with cultured mesenchymal cells delivered through intracoronary infusion, resulting in improvement in end-systolic volume, circumferential shortening, and infarct size [21]. These investigators subsequently examined the use of mesenchymal stem cells in patients with chronic ischemia [22]. In this study, patients who received implantation of autologous bone marrow-derived mesenchymal cells showed significant improvement in perfusion by SPECT imaging, increased exercise tolerance and NYHA functional class, and increased ejection fraction from baseline of 26 ± 6% to 37 ± 9% at 3 months [22]. The POSIEDON trial compared autologous and allogeneic bone marrow-derived mesenchymal stem cell transplantation in a dose-escalating fashion in patients with ischemic cardiomyopathy and LV dysfunction [23]. At thirteen months of follow up, favorable LV reverse remodeling as measured via the sphericity index, and reduction of myocardial infarct size, was seen in both allogeneic and autologous cell treated patients. However, a significant change in LV ejection fraction was not observed. It was also noted that lower doses of administered mesenchymal stem cells were associated with the greatest reduction in LV volumes. In the TAC-HFT trial, subjects received mesenchymal or bone marrow-derived stem cells with 6-minute walk distance, infarct size reduction and regional myocardial function improved in the mesenchymal cell therapy group though no changes in left ventricular chamber volumes or ejection fraction were observed compared to placebo [24]. These results provide useful insight into the feasibility and continued clinical development of mesenchymal stem cells as a potential cardiac cell based therapy.

Cardiac derived/resident stem cells

Once thought to be terminally differentiated, it is now widely accepted that the adult myocardium contains small populations of cardiospheres or clusters of surviving resident cardiac stems cells/ progenitor cells capable of differentiating into cardiomyocytes or vascular lineages. Though such cell lines isolated from myocardial biopsy and have high proliferative capability, endogenous populations of these cells cannot compensate for the magnitude of

ISSN: 2332-3671

injury that typically occurs during an acute myocardial infarction. However, harvesting and expansion of these cells may provide a useful therapeutic source for cardiac repair [2,25]. Cardiac stem cells have been identified by expression of various cell surface markers, including c-kit, Sca-1 and Isl-1. In 2003, Beltrami et al. published the first report of the discovery of endogenous stem cells recovered from the mammalian heart marked by the tyrosine kinase receptor c-kit [26]. Subsequent preclinical trials in animal models demonstrated the safety and efficacy of cardiac stem cell transplantation, thereby leading to the first human trial examining the utility of cardiac-derived stem cells obtained via surgical biopsy specimens for the treatment of post infarction left ventricular dysfunction: SCIPIO [27]. At 12-month follow up, the treatment group receiving intracoronary injection of cardiac stem cells had a marked improvement in LVEF as compared to the medical therapy group (from 27.5 ± 1.6% to 41.2 ± 4.5% [p=0.013]). Also observed were similar trends in NYHA functional class and quality of life indicators that persisted in those completing 24 month follow up. Infarct regression was also demonstrated by cardiac MRI after in those subjects receiving cell therapy. In addition, no significant difference in adverse events was observed between the treated and untreated groups.

The CADUCEUS trial investigated the use of cardiac-derived cells for the treatment of ischemic heart disease, enrolling patients with recent myocardial infarction (< 4 weeks) and LV systolic dysfunction [28]. Patients were randomized to receive cell-based therapy versus standard medical therapy. In the treatment group, intracoronary delivery of cardiac-derived stem cells was performed from 1.5-3 months post-enrollment. A significant regression of infarct mass and increased viable tissue was detected by MRI in the treatment group compared to control. No significant difference was noted in ventricular volumes or ejection fraction between groups. While these results are promising, larger randomized controlled trials are necessary to better define the long term efficacy and clinical utility of cardiac-derived cell therapy in this population.

Methods of Cell Delivery

The various modes of cell delivery and the timing of cellular injection represent salient areas of clinical investigation and research development. The majority of intravenously delivered stem cells are confined to the liver and lungs, with less than 1% of infused cells detected within the infarcted heart at 4 hours [29]. However, anti-inflammatory and pro-angiogenic proteins produced by mesenchymal stem cells trapped in extracardiac tissues potentially may produce beneficial effects on the heart, as evidenced by improvement in cardiac function following intravenous delivery of allogeneic mesenchymal stem cells [30].

Intracoronary infusion of cellular suspension directly into a culprit coronary artery vessel is the most frequently used mode of delivery for stem cells in acute myocardial infarction. Similar to intravenous cellular administration, only about 1-3% of intracoronary delivered cells are retained within the myocardium, with most of the residual being distributed to the liver and lungs. In addition, intracoronary infusion of large cell lineages such as skeletal myoblasts and cultured mesenchymal cells may be associated with mircoinfarction due to vascular obstruction [29].

Direct intramyocardial injection of stem cells has been associated with improved myocardial retention without compromise of coronary blood flow. This method of cellular delivery has been investigated primarily in patients with chronic ischemic disease and LV systolic dysfunction. Intramyocardial cell delivery is typically accomplished via catheter-based percutaneous endoventricular injection, transepicardial approach, or delivery through one of the cardiac veins directly into the myocardium. A specific advantage of percutaneous endoventricular injection is the possibility of real-time 3-dimensional electromechanical mapping to identify and target regions of the myocardium based upon myocardial viability and contractility [31]. In experienced hands, myocardial cell retention is upwards of 20-30% via catheter based endoventricular delivery [32].

Ongoing research is warranted to determine not only the appropriate cell type and method of cell delivery for cardiac based stem cell treatments, but also to determine the optimal timing of stem cell transplantation. A retrospective analysis of the REPAIR-AMI study demonstrated that a clinical benefit was observed only in those patients receiving bone marrow mononuclear cells 5-7 days after infarction [17]. Additional studies such as the LateTIME trial showed that delayed delivery of autologous bone marrow mononuclear cells 2-3 weeks post-myocardial infarction did not demonstrate improvement in LV function at 6 month follow up [18]. The SWISS-AMI trial, which compared post-infarction intracoronary infusion of autologous bone marrow mononuclear cells at 5-7 days or 3-4 weeks, failed to demonstrate benefit on LVEF or infarct size at 4 months assessed by MRI, regardless of timing of delivery [33].

Clinical Application of Stem Cell Therapy in Cardiovascular Disorders

Acute myocardial infarction

Combined data from numerous trials have validated the safety and early efficacy of intracoronary infusion of bone marrow-derived stem cells as adjunctive therapy following acute myocardial infarction (Table 1). The largest randomized studies to date include the BOOST trial [16], TOPCARE-AMI [15] and studies by Chen et al. [21]. In the BOOST trial, treatment with bone marrow-derived cells resulted in 6% relative improvement in EF at 6 months compared to control, and the improvement was maintained at 18 months. These benefits were noted in addition to those derived from standard interventional and medical care following acute myocardial infarction. Reductions in infarct size and LV end diastolic volume, however, were not observed suggesting a possible limitation of bone marrow-derived cells to modulate LV remodeling [16]. In TOPCARE-AMI, patients were randomized to receive either mononuclear bone marrow-derived cells or blood-derived progenitor cells. An 8% relative improvement in LVEF and a reduction in infarct size were observed at 4 month follow up in the cell therapy groups [15]. One of the largest multicentered randomized controlled trials to date, REPAIR-AMI (n=204), demonstrated improvement in LV function following intracoronary infusion of bone marrow-derived mononuclear cells, with benefits persisting at 5 years post-infusion follow up [17,28].

Non-revascularizable coronary artery disease

Despite advanced percutaneous and surgical techniques, a specific subset of patients with chronic ischemic heart disease

ISSN: 2332-3671

Table 1: Major randomized and/or landmark trials in cardiac stem cell therapy: Acute myocardial infarction.

Study	Phase	Design	*n*	Cell Type	Mode of Delivery	Primary Outcome	Results	Trial Number
BOOST	I	RDBPC	60	BM-MNC	IC	LVEF	LVEF↑	NCT00224536
LEUVEN-AMI	II	RDBPC	67	BM-MNC	IC	LVEF	LVEF - , infarct size ↓	NCT00264316
AST-AMI	II	RSBPC	100	BM-MNC	IC	LVEF	LVEF -, LVEDV -, infarct size -	NCT00199823
REPAIR-AMI	III	RDBPC	204	BM-MNC	IC	LVEF	LVEF↑, trend toward ↓ mortality	NCT00279175
REGENT	II	ROPC	200	BM-MNC	IC	LVEF	LVEF -, LVESV -, LVEDV -, MACE -	NCT00316381
LateTIME	II	RDBPC	87	BM-MNC	IC	LVEF, regional LV function	LVEF -, regional LV function -	NCT00684060
TIME	II	RDBPC	120	BM-MNC	IC	LVEF, regional LV function	LVEF -, regional LV function -	NCT00684021
SWISS-AMI	II	ROPC	200	BM-MNC	IC	LVEF	LVEF - , infarct size -	NCT00355186
REGEN-AMI	II/III	RDBPC	100	BM-MNC	IC	LVEF	Ongoing	NCT00765453
BAMI	III	ROPC	3000	BM-MNC	IC	All cause death	Ongoing	NCT01569178
PreSERVE-AMI	II	RDBPC	160	CD34	IC	serious adverse events, myocardial perfusion	Ongoing	NCT01495364
STEMMI	II	RDBPC	78	MSC	IC	Safety	No increased adverse events	NCT00135928
APOLLO	I/II	RDBPC	13	MSC	IC	Safety	LVEF↑, perfusion defect ↓, myocardial scar ↓	NCT00442806
ADVANCE	II/III	RDBPC	360	MSC	IC	Safety, infarct size	Ongoing	NCT01216995
ENACT-AMI	II	RDBPC	100	EPC	IC	LVEF	Ongoing	NCT00936819
Mesoblast AMI/ AMICI		RSBPC	25	MSC	IM	Feasibility, Safety	Ongoing	NCT00555828
PROCHYMAL	II	RDBPC	220	MSC	IV	Safety, LVESV	Ongoing	NCT00877903

RDBPC: Randomized Double Blinded Placebo Controlled; RSBPC: Randomized Single Blinded Placebo Controlled; ROPC: Randomized Open-labeled Placebo Controlled; RONPC: Randomized Open-labeled Non-placebo Controlled; BM-MNC: Bone-marrow Mononuclear Cells; MSC: Mesenchymal Stem Cell; EPC: Endothelial Progenitor Cell; IC: Intracoronary; IM: Intramyocardial; IV: Intravenous; LVEF: Left Ventricular Ejection Fraction; LVESV: Left Ventricular; End Systolic Volume; LVEDV: Left Ventricular End Diastolic Volume; MACE: Major Adverse Cardiac Events

may have no options for revascularization. Such individuals may continue to experience refractory angina in addition to myocardial dysfunction with an increased risk of arrhythmia and sudden cardiac death. Transmyocardial injection of stem cells directly into ischemic myocardium via electromechanical mapping guidance was shown to result in improvement of angina symptoms, exercise capacity, regional tissue perfusion and LV systolic function in several small, nonrandomized studies [34]. The PRECISE trial was a randomized controlled study using adipose-derived stem cells to treat non-revascularizable ischemic myocardium that demonstrated an improvement of maximum oxygen consumption by 3.4 ml/kg/min and a decrease in infarcted myocardium by 8.2% compared to placebo at 6 month follow up [35]. Larger randomized controlled trials are currently underway with evidence of promising preliminary findings [27]. One such trial, ixCELL DCM (NCT01670981), is a multicentered, randomized, double-blinded, placebo controlled phase II study designed to evaluate the efficacy and safety of catheter-based intramyocardial injection of ixmyelocel-T cells in patients with heart failure due to ischemic dilated cardiomyopathy in whom revascularization in not a reasonable option. Ixmyelocel-T cells are refined autologous hematopoietic cells derived from expanded bone marrow lineages including mesenchymal cells, monocytes and macrophages. The primary outcome measures for this study include all-cause death, cardiovascular hospitalizations, and unplanned outpatient or emergency department visits to treat acute decompensated heart failure over a 12 month follow up period post-treatment. Additional secondary outcomes will include functional assessment via 6-minute walk test, quality of life measures and NYHA classification. Table 2 outlines the major clinical trials evaluating the utility of cell therapy in ischemic cardiomyopathies.

Left ventricular systolic dysfunction and congestive heart failure

Randomized, double blind control trials have until recently remained lacking in definitive conclusions regarding the efficacy and long-term benefits of cell based therapy for ischemic cardiomyopathy. However, the recently published C-CURE (Cardiopoietic stem Cell therapy in Heart Failure) trial was a prospective, multicentered randomized trial comparing patients receiving standard medical care versus standard care plus adjunctive cell-based therapy [36]. Human bone marrow cells were harvested followed by mesenchymal stem cell isolation, expansion, lineage specification, and cardiopoietic cell expansion. A total of 47 patients were randomized to endocardial injection of cells versus standard of care. Three-dimensional electromechanical mapping was used to define areas of viable and dysfunctional myocardium. Cardiac function assessed by echocardiography demonstrated a 7% increase in LVEF at 6 months in the cell therapy group (from 27.5 ± 1.0% to 34.5 ± 1.1%) while

ISSN: 2332-3671

Table 2: Major randomized and/or landmark trials in cardiac stem cell therapy: Ischemic cardiomyopathy.

Study	Phase	Design	*n*	Cell Type	Mode of Delivery	Primary Outcome	Results	Trial Number
MAGIC	II	RDBPC	97	SM	IM	MACE, LVEF	↑ exercise capacity, ↑LVEF, improved perfusion (↑ISR in G-CSF arm)	NCT00102128
SEISMIC	II	ROPC	40	SM	IM	Safety, LVEF	LVEF -	NCT00375817
MARVEL	III	RDBPC	170	SM	IM	Safety, QOL, 6 min walk at 1 year	trend toward improved functional capacity, increased occurrence VT	NCT00526253
ESCAPE	III	RDBPC	250	BM-MNC	IM	Survival at 1 year	LVEF↑, improved NYHA class, improved survival at 1 year	NCT00841958
PERFECT	III	RDBPC	142	CD133	IM	LVEF	Ongoing	NCT00950274
FOCUS	II	RDBPC	92	BM-MNC	IM	LVESV, MVO2, reversible defect	LVESV-, MVO2-, reversible defect -	NCT00824005
TAC-HFT	I/II	RDBPC	60	MSC/BMC	IM	serious adverse events	Ongoing	NCT00768066
PROMETHEUS	I/II	RDBPC	45	MSC	IM	serious adverse events	Ongoing	NCT00587990
C-CURE	III	RSBPC	240	MSC	IM	LVEF	LVEF↑, LVESV↓, 6-min walk +, ↑event free survival, improved NYHA class	NCT00810238
RENEW	III	ROPC	291	CD34/G-CSF	IM	exercise tolerance at 1 year	Ongoing	NCT01508910
ACT34-CMI	II	RDBPC	109	CD34	IM	angina frequency	angina frequency↓, exercise tolerance↑	NCT00300053
CADUCEUS	I	RONPC	31	CDC	IC	serious adverse events	SAE-, LVEF - , scar mass↓	NCT00893360
SCIPIO	I	RONPC	40	c-kit+	IC	serious adverse events	SAE-, LVEF↑, infarct size↓	NCT00474461
ALLSTAR	I/II	RDBPC	274	CDC	IC	serious adverse events, infarct size	Ongoing	NCT01458405
REPEAT	II/III	ROPC	676	BM-MNC	IC	Mortality	Ongoing	NCT01693042
IMPACT-CABG	II	RDBPC	20	CD133+	IM	serious adverse events, major arrhythmia	Ongoing	NCT01033617
ixCELL DCM	II	RDBPC	108	ixmyelocel-T	IM	all cause death, CV hospitalization	Ongoing	NCT01670981

RDBPC: Randomized Double Blinded Placebo Controlled; RSBPC: Randomized Single Blinded Placebo Controlled; ROPC: Randomized Open-Labeled Placebo Controlled; RONPC: Randomized Open-labeled Non-placebo Controlled; BM-MNC: Bone-Marrow Mononuclear Cells; MSC: Mesenchymal Stem Cell; SM: Skeletal Myoblasts; CDC: Cardiac Derived Cells; G-CSF: Granulocyte Colony-stimulating Factor; IC: Intracoronary; IM: Intramyocardial; IV: Intravenous; LVEF: Left Ventricular Ejection Fraction; LVESV: Left Ventricular End Systolic Volume; SAE: Serious Adverse Events; NYHA: New York Heart Association Functional Class; QOL: Quality Of Life; ISR: In-stent Restenosis; MVO_2: Maximal Oxygen Consumption; CV: Cardiovascular

remaining essentially unchanged in the control group. In addition, cell therapy significantly reduced LV end systolic volume and improved 6-minute walk distance, NYHA functional class and quality of life as determined by the Minnesota Living with Heart Failure Questionnaire. This study was the first of its kind to demonstrate the potential of cardiogenic lineage-guided cell-based therapy to regenerate myocardium in patients with ischemic heart failure.

Results were recently reported from the TAC-HFT trial, a randomized, blinded, placebo controlled study enrolling 65 patients with ischemic cardiomyopathy and LV systolic dysfunction [24]. Subjects receiving transendocardial injection of mesenchymal or bone marrow-derived stem cells were compared to placebo-treated subjects and followed for 1 year. Quality of life indicators were improved in both cell therapy groups; however, 6-minute walk distance and infarct size was reduced only in the mesenchymal cell therapy group. Despite these findings, no changes in left ventricular chamber volumes or ejection fraction were observed.

The role of stem cell therapy for cardiac repair in nonischemic cardiomyopathies is not yet been clearly defined though several small, randomized controlled trials involving intracoronary infusion of bone marrow derived cells or autologous CD34+ cells have demonstrated improvements in ejection fraction [37]. Table 3 outlines the major clinical trials evaluating the use of cardiac stem cell therapy for nonischemic cardiomyopathies. Additional trials evaluating stem cell therapy in dilated, nonischemic cardiomyopathies are currently underway including REGENERATE-DCM (NCT01302171), a multicenter double-blinded randomized controlled study examining the role of autologous bone marrow-derived cells and granulocyte colony stimulating factor (G-CSF) to improve cardiac function in dilated cardiomyopathy. Another such double-blinded, randomized, sham-procedure controlled phase III trial is currently enrolling a projected 1730 subjects with left ventricular systolic function of either ischemic or nonischemic etiology to determine whether transendocardial delivery of allogeneic human bone marrow-derived mesenchymal precursor cells (CEP-41750) are effective in treating

ISSN: 2332-3671

Table 3: Major randomized and/or landmark trials in cardiac stem cell therapy: Non-ischemic cardiomyopathy/Dilated cardiomyopathy.

Study	Phase	Design	*n*	Cell Type	Mode of Delivery	Primary Outcome	Results	Trial Number
POSEIDON-DCM	I/II	RONPC	30	MSC	IM	serious adverse events	SAE -, auto/allo: infarct size ↓, LVEF -, allo: 6-min walk test ↑, QOL↑	NCT01087996
REGENERATE-DCM	II	RDBPC	60	BM-MNC vs placebo/G-CSF	IC	LVEF	Completed (results pending)	NCT01302171
NOGA-DCM	II	RSBPC	90	CD34	IC/IM	LVEF	Ongoing	NCT01350310
IMPACT-DCM	II	ROPC	40	CDC	IM	Safety	Completed (results pending)	NCT00765518
TOPCARE-DCM	II	RONPC	30	BM-MNC	IC	LVEF	Completed (results pending)	NCT00284713
CEP-41750 (Teva)*	III	RDBPC	1730	allogeneic MPC	IM	HF-MACE	Ongoing	NCT02032004

RDBPC: Randomized Double Blinded Placebo Controlled; RSBPC: Randomized Single Blinded Placebo Controlled; ROPC: Randomized Open-labeled Placebo Controlled; RONPC: Randomized Open-labeled Non-placebo Controlled; BM-MNC: Bone-Marrow Mononuclear Cells; MSC: Mesenchymal Stem Cell; CDC: Cardiac Derived Cells; G-CSF: Granulocyte Colony-stimulating Factor; IC: Intracoronary; IM: Intramyocardial; LVEF: Left Ventricular Ejection Fraction; SAE: Serious Adverse Events; MPC: Mesenchymal Precursor Cells; HF-MACE: Heart Failure Major Adverse Events; *Study Evaluates Both Ischemic and Non-ischemic Cardiomyopathy

chronic heart failure, with primary outcome measure of time to first heart failure related major adverse cardiac events over a 5 year study period (NCT02032004).

Conclusions

Substantial advances in cell-based therapy for cardiac disease have evolved over the past decade. Numerous small clinical trials conducted to date have demonstrated modest but encouraging results in terms of clinically accepted endpoints such as recovery of LV systolic function and improvement in quality of life. Over 50 phase I/II trials have demonstrated the use of cell based therapy in the treatment of acute myocardial infarction or chronic heart failure to be both safe and clinically feasible with combined data analysis indicating effectiveness in improvement of ejection fraction and reduction of infarct size [27].

Despite these promising findings, a variety of considerations continue to challenge widespread adoption of cell-based therapies for the treatment of cardiovascular disease. Key concepts such as optimum cell type, timing and method of delivery, and retention of transplanted cardiac cells into host myocardium, pose challenges that must be elucidated prior to widespread implementation of cell therapy in the clinical arena [38].

Currently, clinical cardiovascular guidelines do not include cardiac cell therapies as standard of clinical care and no cell products are commercially available in the US. Ongoing large phase III clinical trials may provide the critical evidence needed for cell therapy to become part of the armamentarium available to treat advanced cardiovascular diseases.

Future Directions

In its infancy, cardiac stem cell research focused primarily on the replacement of damaged or lost cardiomyocytes. More recently, contemporary cardiac cellular therapy has shifted to the concept of modulating cytokine release and paracrine-related cellular repair. The cytokine-paracrine model considers the primary function of transplanted cells to be enhancement of angiogenesis, reduction of inflammatory responses, and metabolic modulation leading to improved tissue perfusion, reduction of apoptosis and activation of resident cardiac stem cells. Together, these functions lead to increased cellular repair and cytoprotection, with little if any role for the transplanted stem cells themselves to differentiate into cardiomyocytes [6]. Limited retention and survival of transplanted stem cells remains a significant barrier to improving the efficacy of cardiac regenerative therapy. Research into mechanisms to enhance cell homing, migration, and retention include preconditioning or priming of stem cells via induction of ischemia, treatment with pharmacologic reagents and growth factors, hypoxic shock or genetic manipulation to promote cellular resistance and survival against oxidative stress [39]. Such studies are currently underway in several clinical trials including ENACT-AMI, which examines the potential improvement after transplantation of cells transfected with human endothelial nitric oxide synthase (NTC00936819), and the ALCADIA trial (NCT00981006), which incorporates growth factor treatment as a strategy to enhance the reparative capacity of stem cells [7].

Studies thus far have validated the safety of most cardiac cell-based therapies, although patient protection must remain of utmost importance as continued advancements coupled with increased cell retention, survival and regeneration of transplanted cells may alter the clinical course. Ongoing consideration for patient safety in regards to potential arrhythmogenesis, oncogenicity and aberrant cell differentiation, multiorgan seeding and accelerated atherosclerosis must be reevaluated with advancing cell-based therapies [6,38].

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