

Stem Cell Therapy: Promising Treatment in Heart Failure?

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Abstract Cardiac repair through the use of regenerative medicine has been a considerable research focus over the last decade. Several stem cell types have been investigated over this timeframe as potential candidates to target post-infarction heart failure. The progression of investigation through the rigors of clinical trial design has provided some answers as to the potential clinical utility of this therapy; although there are many questions that remain. This review will concentrate on the clinical trial results of stem cell therapy for cardiac repair since the turn of the century and discuss some of the points that need clarification before this form of therapy can be considered for widespread applicability.

Keywords Stem cell therapy · Bone-marrow mononuclear stem cells · CAD · Chronic ischemic heart disease · Myogenesis

Introduction

According to the WHO, cardiovascular disease is related to 30 % of global mortality making it the single most contributory cause of death worldwide. In the U.S., coronary heart disease accounts for approximately 16.9 million cases annually [1•]. There are approximately 5.3 million patients who currently have heart failure in the U.S. In the ARIC study, over an average of 17.6 years of follow-up, one in

three African American and one in four Caucasian participants were hospitalized with heart failure [2]. The mechanisms of heart failure are multi-faceted; however, an underlying cause, particularly in ischemic cardiomyopathy, is the presence of scar tissue and the loss of viable, functioning myocytes which actively contribute to the contractility and relaxation of the ventricle. The majority of treatment options (medical therapy, catheter-based or surgical revascularization for earlier stages and mechanical support for later stages) employ a strategy to limit further scar formation and adverse remodeling while enhancing the function of salvaged myocardium [3, 4]. While some therapies have improved mortality and provided symptomatic relief, the issue of transforming non-viable scar tissue to functional, biologically relevant cells remains a “holy grail”. Moreover, the cost of treating heart failure with our current standard-of-care armamentarium makes this condition the most expensive of Medicare diagnoses [5]. Hence, the need to find a more enduring, definitive therapy is of utmost importance. To this end, the scientific community has embarked on a path of discovery in the field of stem cell therapy. The initial clinical experiences reported were those using precursor bone marrow cells and have shown some interesting findings as promising results have been garnered in both pre-clinical and clinical studies. Since these earlier studies, newer stem cell types from various sources have been identified and have now been more thoroughly characterized. These newer cell types will most likely bring about a second wave of clinical studies as seen between the years of 2004 – 2006. Moreover, the methods used to study the effect of the cells continue to evolve and bring light to mechanistic potentials. Together, both with rapid translation of cellular therapy to the clinical realm and significant inroads made in the methods by which therapeutic effects are measured, it will indeed suffice to say that adult stem cells have shown a great deal of promise and will continue to do so as the field develops [4]. Herein, a review

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of clinical stem cell studies in patients with heart failure is presented while an attempt to address controversies and gray areas is also undertaken. (Figure 1)

Skeletal Myoblasts

The first description of the use of stem cells for the purpose of cardiac repair in humans came from Menasche et al. in 2001 [6••]. A patient with ischemic cardiomyopathy received epicardial transplantation of 800 million autologous skeletal myoblasts (SKM) at the time of coronary artery bypass graft (CABG) surgery. At 5 months follow-up they reported a

significant improvement in left ventricular (LV) function and viability. This initial experience propelled a Phase I investigation, performed by the same investigators, in which 10 patients were consecutively enrolled to receive SKM at the time of CABG [7]. Compared against a consecutively enrolled control group receiving standard medical therapy, they found improvements in cardiac function and functional capacity. However, they reported four patients experienced “delayed” episodes of ventricular arrhythmias. Despite these safety concerns, a Phase II investigation, the MAGIC trial, was carried out in which 97 patients were enrolled and randomized to receive 400 million SKM, 800 million SKM, or medical therapy [8]. No significant

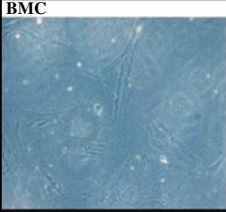
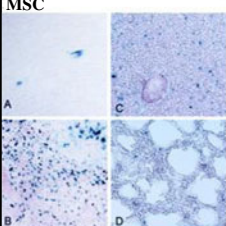
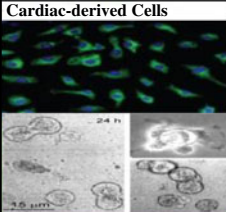
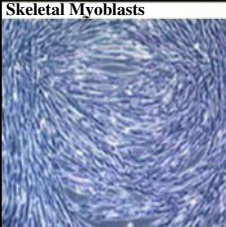
CELL TYPES	REPORTED ROUTES OF ADMINISTRATION	THERAPEUTIC EFFECTS REPORTED	POTENTIAL CLINICAL ADVANTAGES	POTENTIAL CLINICAL CHALLENGES
	Intracoronary Transendocardial Epicardial	Increased global and regional function (10-14) Increased functional capacity (10-14) Regression of infarct size (12, 13)	Many clinical centers have experience with harvest technique (10-19) Cell processing does not require ex vivo manipulation (10-19) Cell implantation can be performed in the setting of acute MI (10-19)	Exogenous progenitors at varying levels of commitment (10-19) Progenitors are a small % of unfractionated BMC (10-19) Conflicting results describing functional benefit (10-19)
	Intracoronary Intravenous	Increased global and regional function (33) Increased functional capacity (30) Improved pulmonary function with intravenous infusion (28)	“Immunoprivileged” (33) Simple isolation and culture process (27-30)	Large diameter of cells limits transplantation (27-30) Lineage restriction (24, 25)
	Intracoronary	Increased global and regional function* (41) Increased functional capacity (41) Regression of infarct size (41, 43)	Isolation from biopsy samples** (39-43) Robust growth kinetics (39-43) Simple isolation and expansion process (39-43)	Autologous cells requiring expansion† (39-43) Safety data comes from small, pilot trials (42, 43)
	Epicardial	No significant changes in global or regional function noted between test groups (8, 9)	Minimally invasive tissue harvest (6-9) Rapid expansion of cell culture (6-9)	No functional benefit demonstrated to date (8, 9) Arrhythmia concerns (7, 8)

Fig. 1 Overview of stem cell types utilized for cardiac repair. * Cardiac stem cells only. ** CSC isolated from atrial biopsy, CDC from endomyocardial biopsy. † CDC have been studied for allogeneic potential. BMC Image: from Lin GS, et al., “Autologous transplantation of bone marrow mononuclear cells improved heart function after myocardial infarction,” *Acta Pharmacologica Sinica*, Volume 25, Issue 7, with permission from Nature Publishing Group. MSC Image: from Catalin T, et al., “Human Mesenchymal Stem Cells Differentiate to a Cardiomyocyte Phenotype in the Adult Murine Heart,” *Circulation*, Volume 105, Issue 1, with permission from Wolters Kluwer Health.

Cardiac-derived Cells Image: from Bolli R, et al., “Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial,” *The Lancet*, Volume 378, Issue 9806, with permission from Elsevier; and from Messina E, et al., “Isolation and Expansion of Adult Cardiac Stem Cells From Human and Murine Heart,” *Circulation Research*, Volume 95, Issue 9, with permission from Wolters Kluwer Health. Skeletal Myoblasts Image: from Haider HKH, et al., “Myoblast Transplantation for Cardiac Repair: A Clinical Perspective,” *Molecular Therapy*, Volume 9, Issue 1, with permission from Nature Publishing Group

change in cardiac function was observed and, more importantly, the trial was terminated early secondary to an increased number of ventricular arrhythmias in the treatment groups. Subsequently, a Phase IIa clinical investigation, the SEISMIC trial, was performed demonstrating no difference in ventricular arrhythmias between treatment and control groups, although all patients were placed on prophylactic antiarrhythmic medications [9]. Furthermore, no change in cardiac function was noted between groups. It is now generally accepted that SKM remain functionally isolated from host myocardium due to an inability to express functional proteins crucial for the appropriate propagation of electrical conduction.

Bone Marrow Mononuclear Cells

The cardiovascular research community has gained the greatest insights and experience through the use of bone marrow-derived progenitor cells (BMC) for cardiac repair. There are two very practical reasons these cells have received the greatest attention; first, the medical community has a wealth of experience with the harvest of progenitor cells from this tissue compartment, and secondly, there is no time-consuming process required for the ex-vivo manipulation of cells prior to clinical use. The first clinical trial of stem cell transplantation for the treatment of post-infarction left ventricular dysfunction was carried out by Strauer et al. in 2002 [10••]. Ten patients were consecutively enrolled to receive intracoronary infusion of BMC into the infarct-related artery (IRA) at ~5 days after acute myocardial infarction (MI). At 4 months follow-up they found significant improvement in global and regional ventricular function with concomitant improvement in myocardial perfusion. Most importantly, no significant differences in adverse events were noted when compared to a control group receiving standard medical therapy alone.

This seminal investigation acted as a springboard from which several investigations catapulted into the medical literature over the early part of the last decade. The overwhelming majority of clinical trials performed utilizing BMC for the treatment of LV dysfunction were carried out in a similar patient population; intracoronary infusion of BMC into the IRA at 5 – 9 days after first acute MI. The TOPCARE-AMI trial enrolled 20 patients randomized to receive either circulating progenitor cells (CPC) or BMC [11]. At 4 months follow-up the investigators noted an 8 % improvement in ejection fraction (EF). The BOOST trial, a randomized control trial, enrolled 60 patients randomized to receive BMC or medical therapy [12]. At 6 months follow-up, the treatment group demonstrated a 6.7 % improvement in EF compared to 0.7 % for the controls. The REPAIR-AMI trial, a placebo-controlled, randomized clinical investigation, enrolled ~200 patients to receive BMC or placebo [13]. At 6 months follow-up, the treatment group demonstrated a 5.5 % improvement in EF compared to a 3.0 % increase in the control group. The

important observation within these findings is the inverse relationship between increasing rigor of clinical trial design and diminishing treatment effect observed. Fueling the fire for the debate of clinical utility of BMC was negative results of clinical investigations such as the ASTAMI trial [14] and the BOOST 18 months follow-up [15]. More recently, results from two separate trials of BMC in AMI have been revealed showing no difference between control and treated patients [16, 17]. In 2011, an investigation of BMC transplantation at 2 – 3 weeks after MI was undertaken in the double-blind, placebo-controlled Late TIME trial. No improvement was noted in regional or global function at 6 months follow-up [18].

However, analysis of cohort studies and randomized clinical trials has shown a modest benefit in favor of BMC in the treatment of patients suffering from LV dysfunction post-MI [19•]. Combining this modest efficacy data with a favorable safety profile, the first Phase III clinical trial of any cell type is poised to begin enrollment. The BAMI trial is designed to enroll 3,000 patients to be randomized to therapy with BMC or medical therapy. [NCT01569178] The primary outcome is investigation of the time from randomization to death. If a survival benefit is demonstrated, the medical community may witness the first cell-based therapy approved for widespread use in the treatment of post-infarction LV dysfunction.

The results of clinical investigations of BMC therapy in chronic MI are strikingly similar. Although positive results in trials such as IACT[20], STAR-Heart[21], and TOPCARE-CHD[22] have been notable, equivocal results have been demonstrated in investigations such as the FOCUS trial[23].

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are a subset of bone marrow cells which are characterized by the following criteria: 1) MSCs must be plastic-adherent under standard culture conditions, 2) must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79 or CD19 and HLA-DR surface molecules, and 3) must differentiate to osteoblasts, adipocytes and chondroblasts in vitro [24]. This cell type, while exhibiting some similar biologic reparative effects similar to bone marrow mononuclear cells, have distinct advantages as they are hypogenic (or as they have more recently been coined, “immunoprivileged”[25]), most likely secondary to their lack of HLA class II expression [26]. The cell type, therefore, shows a great deal of promise as an “off-the shelf” product with the possibility of allogeneic product administration. More recently, clinical data using allogeneic preparations have been presented with promising results. These, along with earlier, foundational studies are presented here.

One of the earliest clinical trials which employed MSCs in the acute myocardial ischemia setting was reported by Chen et al. In this study, 69 patients were randomized to

either mesenchymal stem cell or saline (vehicle) treatment. Preparation of the MSCs was done by bone marrow aspiration and culturing for 10 days. Following successful percutaneous revascularization, the cells were infused through the culprit vessel. Follow-up occurred 3 months after implantation which included PET and echocardiographic imaging. Improvements in the end-systolic volume, circumferential shortening, and infarct size were noted as a result of the therapy [27]. Upon its publication, correspondences emphasized the significance of the reported results [28]; specifically the improvement in global LVEF was higher than that which was reported in the BOOST trial, a study which studied intracoronary administration of bone-marrow mononuclear cells [12].

A smaller trial done by Katristsis et al. was conducted using autologous endothelial progenitor cells and MSCs cultured in vitro for 7 days prior to transplantation in patients who had experienced an antero-septal MI with subsequent percutaneous stent placement. Stress echocardiography revealed an improvement in myocardial contractility in segments which were previously deemed nonviable along with improvements in infarct size by sestimibi thallium studies. It must be noted here, however, that the study was done in patients with recent and old antero-septal MIs, as average time from MI to cell administration was 242.4 ± 464.0 days [29]. A difference in effect size by the age of the infarct was not specifically studied. An interesting feature of the study is that MSCs were co-cultured with endothelial progenitor cells, effects of which are not yet fully defined.

Mesenchymal stem cells were also studied in patients with chronic ischemia by Chen et al. [30] In this study, 22 patients received implantation of autologous BM-MSCs and were followed for 12 months. Reversible defect size in the cell therapy group decreased from 16 ± 8 % at baseline to 6 ± 2 % at 12 months. Exercise tolerance also showed enhancement 3 months after cell therapy (5 ± 2 METS at baseline vs. 7 ± 3 METS at 3 months) with improvement of NYHA function class. (2.7 ± 0.8 at baseline vs. 1.6 ± 0.1 at 3 months). LVEF also increased significantly from 26 ± 6 % at baseline to 37 ± 9 % at 3 months.

The issue of arrhythmogenicity stemming from the adverse electrophysiologic milieu of heart failure continues to be a major focus of research and therapy [31] due to its contribution to morbidity and mortality. Interestingly, MSCs have been studied in this regard in preliminary fashion. Katristsis et al. transplanted MSCs with EPCs in five patients with a history of previous antero-septal myocardial infarction and a history of ventricular arrhythmias requiring internal defibrillator (ICD) implantation. Three patients showed evidence of improvement in regional wall motion after cell transplantation. Furthermore, interrogation of the ICD at 16–36 months follow-up revealed no episodes of non-sustained/sustained ventricular arrhythmia in any of the

patients. However, sustained ventricular arrhythmia was induced in two patients post cell therapy [32]. While this was a small pilot study, its focus on MSC administration as a potential antiarrhythmic therapy is both promising and novel.

However, more definitive, larger studies are both underway and resulted by Dr. Hare and his group. Of note, the team has studied both autologous and allogeneic delivery preparations of MSCs in the setting of heart failure [33]. The POSIEDON study best illustrates the effect of both in a single trial. As a Phase 1/2 study, they compared the safety and feasibility of allogeneic MSCs *viz a viz* with autologous MSCs in patients with ischemic cardiomyopathy. Additionally, three doses (20, 100 and 200 million) of each cell type were studied in regards to 30-day post-catheterization incidence of serious adverse events and various efficacy assessments which included LV function and geometry, functional capacity and quality of life questionnaire results. Mean LV ejection fraction was 27.1 ± 9.6 % in the allogeneic group and 29.0 ± 8.8 % in the autologous arm. Surprisingly, a trend towards higher adverse events was noted with the autologous arm (33.3 % vs. 6.7 % in the allogeneic arm). For efficacy endpoints, the allogeneic arm showed similar reduction in scar size as the autologous arm (-31.61 %; 95 % CI, -49.24 to -13.99). Moreover, LV remodeling (as measured by the sphericity index - a measure of the globularity of the heart secondary to adverse ischemic remodeling) showed similar improvement in both the allogeneic and autologous arms. These encouraging results seem to suggest that an “off-the-shelf” product is feasible. Larger studies will hopefully buttress these findings further.

Other larger studies have yet to be completed and reported. Of note, the TAC-HFT trial [34] targets patients with chronic ischemic cardiomyopathy in a double-blinded, placebo controlled study using autologous MSCs delivered transendocardially. Likewise, the C-CURE trial [35] has reported data in 45 patients has reported data in 45 patients of which 21 were treated with MSCs pretreated with cytokines to enhance cardiopoiesis. An improvement in the 6-minute walk test and ejection fraction was noted in the treated arm. Final results of both trials are eagerly awaited.

Cardiac-Derived Stem Cells

The clinical dogma regarding the heart as a terminally-differentiated organ without cellular turnover outside of the perinatal period is one that is falling out of favor. Evidence demonstrating the cycling of cardiomyocytes after myocardial infarction in postmortem tissue samples gave cardiovascular investigators the first insight regarding this organ’s potential for cellular regeneration [36]. In 2002, further evidence was brought forth utilizing postmortem analysis of sex-mismatched organ transplant demonstrating the existence of cardiomyocytes of recipient origin in donor

organs [37]. More recently, elegant experimentation using C-14 labeling provided convincing evidence of cellular turnover within the heart [38]. The aforementioned data fuelled the research efforts leading to the discovery of stem cell compartments within the heart. In 2003, Beltrami et al. outlined the initial discovery of cardiac stem cells (CSC) marked by the tyrosine kinase receptor c-kit [39••]. Shortly thereafter, Messina et al. published data regarding the discovery of cardiac-derived stem cells (CDC) utilizing a primary explant technique and principals of spheroid culture [40]. These stem cells were identified by markers such as c-kit, CD105, and CD90. Several preclinical studies followed demonstrating the safety and efficacy of transplantation in animal models of infarction leading to the first ever in-human clinical investigations of cardiac-derived stem cells for the treatment of post-infarction LV dysfunction.

The SCIPIO trial (Stem Cell Infusion in Patients with Ischemic Cardiomyopathy) began enrollment in March 2009 [41••]. After an initial stage of consecutive enrollment to assess short-term safety, patients were randomized to either treatment with CSC or standard medical therapy. The average age of infarct was ~4 years and patients enrolled demonstrated moderate to severe LV dysfunction despite surgical revascularization (LVEF \leq 40 %). CSC were isolated from surgical biopsy samples and expanded prior to infusion. Infusion took place at 4 ± 1 months after surgery. Enrollment is complete and a total of 20 treated and 13 control patients are currently in follow-up. At 12 months, the treated group has demonstrated an 8 % improvement in ejection fraction evaluated by 3D echocardiography as compared to an insignificant change in patients of the medical therapy group. Similar trends in changes in NYHA functional class and metrics of quality of life have been noted. Importantly, these trends of functional benefit seem sustained in those patients that have completed 24-month follow-up. Furthermore, in a subset of patients undergoing MRI, statistically significant infarct regression was demonstrated utilizing separate methodologies [42]. Importantly, no differences in adverse events were noted between groups.

The CADUCEUS trial (Cardiosphere-Derived Autologous Stem Cells to Reverse Ventricular Dysfunction) also began enrollment in 2009 [43••]. Patients with recent myocardial infarction (< 4 weeks prior to enrollment) and mild to severe LV dysfunction (LVEF 25 – 45 %) were eligible for enrollment. After an initial period of consecutive enrollment, patients were randomized to CDC treatment or standard medical therapy. CDC were isolated from endomyocardial biopsy samples and infused from 1.5 – 3 months after enrollment. Enrollment is complete and a total of 17 CDC-treated and eight control patients were reported to be in follow-up. The investigators noted a significant regression of infarct mass and increase in viable cardiac tissue as measured by MRI in treated patients as compared to those receiving standard medical

therapy. No differences in ventricular volumes or ejection fraction were noted between groups. No differences in adverse events were noted between groups either.

This initial experience with cardiac-derived stem cell transplantation for the treatment of ischemic cardiomyopathy has demonstrated the separate therapies have a favorable short-term safety profile and that transplantation procedures are feasible to perform. Larger, more rigorous clinical trials are warranted for critical assessment of efficacy.

Discussion

While a great deal of resources and effort have been dedicated to the study of stem cell bioactivity and potential for clinical intervention over the last decade, stem cell therapy for cardiac repair remains a relatively young science. As with the development of any new discipline, clarification of metrics necessary for the critical assessment of clinical intervention is imperative. A multitude of variables require careful consideration including cell homing, viability, engraftment, and retention. Theoretically, enhancement of these aspects of transplantation should refine the process of delivery and, ultimately, improve clinical outcome. Additionally, consensus is needed within the research community as to the choice of clinical endpoints assessed by investigations of stem cell therapy in order to critically examine the potential efficacy of therapeutic intervention.

The question of finding the “optimal cell type” is an esoteric one and a conversation that is fraught with varying levels of bias. The cell types that have been studied for the treatment of heart failure have merits and limitations. Optimization of timing, route, and other factors surrounding stem cell transplantation are more realistic targets for improving therapeutic outcomes rather than finding the proverbial “magic bullet”. The important information that has been gathered from the clinical investigations performed to date, and one of the only aspects of stem cell therapy that can be agreed upon considering the differences in trial design, is that the majority of cell types studied to date have demonstrated a favorable short-term safety profile.

Optimization of retention and engraftment has been the focus of many preclinical investigations [44–46]. Although the true mechanism of action regarding the capabilities of various stem cell populations for cardiac repair remains a contentious argument, regardless of whether the mechanism is related to direct cardiac regeneration, paracrine effects or activation of endogenous stem cell pools, increased engraftment and retention could potentially improve the magnitude of treatment effect. Timing of cell delivery is one important consideration. In acute MI, molecules related to signaling and cell homing (i.e. SDF-1) are upregulated, indicating that this may be an advantageous timing for optimal cell

retention [47]. However, this is also a period during which the inflammatory response creates an extremely hostile environment detrimental to transplanted cell survival [48]. In order to draw comparisons between timing of cell delivery and levels of retention and how this may affect clinical outcome, the development of safe and efficacious methods of imaging to evaluate cell tracking will be necessary.

Improving levels of retention and engraftment may be related to augmenting other aspects of the cell delivery process. Artificially engineered biological scaffolds have been developed to this effect [49–51]. Preconditioning of cell cultures prior to transplantation is another strategy which may influence resistance to cell death in hostile cellular environs [52–54]. Furthermore, other groups have shown improved engraftment levels by co-culturing stem cell populations with molecules involved in homing [55] and cytokines conferring anti-apoptotic benefit [56]. Regardless of the potential benefit conferred by strategies such as these, more rigorous assessment of safety will be necessary prior to use in human clinical investigations.

Route of delivery has been investigated utilizing intravenous and intracoronary infusion, as well as transendocardial and epicardial injection. Intravenous infusion has been limited to stem cells that have larger diameter (i.e. MSC), and is limited by off-target delivery [57]. Epicardial injection has the distinct advantage of transplantation under direct visualization. This invasive strategy has to be performed at the time of thoracotomy/sternotomy and is not applicable to the majority of patients with heart failure. Intracoronary infusion has been utilized most often in clinical investigations of stem cell therapy. As implied, this method requires patent conduits to the region of interest which may not be feasible in patients with ischemic cardiomyopathy unless they are surgically revascularized. Transendomyocardial injection may overcome these limitations. Guided by electromechanical mapping, precise injections in the border zone of infarcted tissue can be delivered. Although this delivery method is associated with the risk of ventricular perforation, and cells are delivered in clusters to areas of uncertain vascular supply. Beyond the advantages and limitations listed herein, there is not a convincing body of evidence in the way of randomized clinical data available comparing the various methods.

Determination of clinical endpoints with adequate sensitivity and specificity to evaluate incremental improvement above that conferred by standard medical therapy remains a contentious argument amongst investigators. Ejection fraction by echocardiography and determination of perfusion by SPECT imaging have been criticized as lacking the necessary sensitivity required to determine the true effect of stem cell therapy [58]. Cardiac MRI (CMR), especially considering infarct measurement by late gadolinium enhancement, has provided a powerful diagnostic tool for the determination of multiple

functional parameters and scar burden [59, 60]. Although, the safety of CMR in the heart failure cohorts studied, especially concerning the subset with implantable defibrillators, has not reached uniform consensus. Techniques to accurately determine perfusion are also improving with CMR and CT; [61, 62] although PET currently provides the gold standard method for assessing viability, [63–65] and is likely underutilized in stem cell investigations. Other measures of functional status including NYHA class, treadmill times, and metabolic parameters such as VO₂ are fraught with limitations as well. General consensus as to the accepted measures of functional recovery is needed in order to move forward and critically appraise the results of future stem cell investigations.

Conclusion

The discipline of cell-based therapy for cardiac repair has grown immensely over the past decade. Investigations of multiple cell types continue to progress through the rigors of clinical trial designs. Refinement of methodologies and augmentation of technical aspects of transplantation may provide further insights to the true potential of stem cell therapy. Consensus on acceptable clinical endpoints and methodologies used to assess those endpoints are necessary to move forward and critically examine the quality of data gathered in future clinical investigations of stem cell therapy.

Disclosure No potential conflicts of interest relevant to this article were reported.

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