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USE OF STEM CELLS IN HEART FAILURE TREATMENT: WHERE WE STAND AND WHERE WE ARE GOING

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Abstract

End-stage heart failure is the final common pathway of an irreversible process associated with loss of myocardial cells. In this process, the capacity for renewal and repair of myocardial tissue is inadequate and ultimately leads to ventricular remodeling. Novel therapeutic strategies have been developed to prevent it, one being cell therapy, which has emerged as a potential approach to directly repopulate and repair the damaged heart. Here, we review the use of regenerative cell therapy for different cardiac diseases and discuss the positive effect of cell therapy mediated by paracrine factors instead of turning directly into cardiomyocytes.

Introduction

Cardiovascular disease is a major public health problem that imposes a huge economic burden on health systems around the world, and patients with end-stage heart failure (HF) represent a large share of the healthcare spending.[1-3]

End-stage HF is the final common pathway of a process of myocardial cell death triggered by varied etiologies and characterized by myocardial dysfunction and inadequate remodeling. It is a complex and heterogeneous entity with multiple etiologies, from cardiomyopathy (CM) of ischemic origin that can improve with restoration of myocardial perfusion to other infectious, inflammatory or infiltrative processes that are less responsive to current medical treatments. Among these, nonischemic dilated CM represents one-third of all patients with HF and is more prevalent in younger patients, with an annual mortality ranging from 10% to 50%.[4-8]

Despite this, several treatment options such as standard pharmaceuticals, ventricular assist devices, cardiac resynchronization therapy, and cardiac transplantation have remained unchanged for several years.[9-12] Although cardiac transplantation has been shown to improve outcomes in end-stage HF, the procedure comes with inherent risks.[13-15]

It is well known that the heart has no intrinsic muscular regeneration capacity, so regenerative medicine techniques to restore cardiac function are being increasingly investigated as potential options to treat cardiovascular disease. Among these techniques are bone marrow-derived cell (BMC) therapies.[16-17] The following provides a brief review of information available on the safety of regenerative cell therapy for different cardiovascular diseases.

Cellular Cardiac Regenerative Therapies

There is a growing understanding of the anatomical and functional disorders that occur in the myocardial cell in dilated CM, such as endothelial dysfunction, impaired microvascular function (diffuse in the case of nonischemic etiology), inappropriate remodeling, increased intracardiac pressures, and progressive deterioration of ventricular function.[18-19]

Cell-based therapies have rapidly emerged as a potential novel therapeutic approach that attempts to regenerate cardiac myocyte contractility, improve diffuse microvascular dysfunction, and reverse ventricular structural changes such as dilation and fibrosis. In order to reverse or mitigate this cascade of events that adversely affects ventricular function, multiple therapies have been tested, including different cell strains and routes of administration (Figure 1).

Several mechanisms have been described that may explain the effect of cell therapies, such as attenuation of cardiomyocyte and endothelial cell apoptosis, paracrine anti-inflammatory effects, promotion of angiogenesis and activation of progenitor cells *in situ*, increased vascularity, improved endothelial dysfunction,

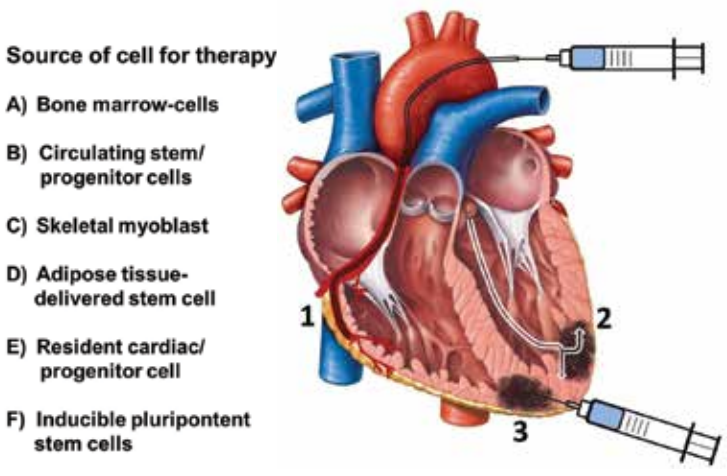

Figure 1. Source of cells and their delivery routes for the treatment of heart disease. (1) Intracoronary infusion; (2) Transendocardial; (3) Epicardial intramyocardial injection.

and decreased myocardial fibrosis.[20-22] However it has also been observed that some factors may adversely affect these effects: the quantity of infused cells, cell viability, the zone of infusion, the delivery route, and, especially, the nesting rate in the myocardial tissue. In this regard, intracoronary infusion has proved to be the most practical, safe, and effective technique to elicit an adequate rate of cell nesting.[23-24] Even so, when used for ischemic heart disease, this procedure has shown conflicting results regarding efficacy and safety. Moreover, stem and progenitor cell-based therapies have been applied at different stages of disease, as in the acute phase of myocardial infarction (MI) or after remote MI with chronic ischemic CM and, more sparsely, for patients with nonischemic dilated CM.[25]

Acute Myocardial Infarction

Acute MI has been the most studied clinical context in which to assess the safety and efficacy of cell therapies; this is based on the principle that the window of time during an acute ischemic insult is the most appropriate opportunity to prevent the death of cardiomyocytes and, therefore, subsequent remodeling (Table 1). Bone marrow cells (BMCs) are the most common cells used for therapy. They are injected into the infarcted vessel after it has been reopened by balloon dilation and stent placement, making this therapy only available to revascularized areas. In this context, it has been demonstrated that after intracoronary infusion, cardiac homing of BMCs increased in patients with an acute MI compared with chronic MI. This effect is probably due to the increased amount of chemoattractant factors secreted from the ischemic tissue and to the potential of BMCs to promote cardiac neovascularization and attenuate ischemic injury.

Other cell lineages have been tested recently, such as the autologous subtypes of tissue-resident cardiac stem and progenitor cells called cardiosphere-derived cells.[26] A phase 1 study reported a reduction in myocardial scar mass and increased viability mass but with no effect on left ventricular ejection fraction (LVEF) at 6 months.[27-29] A recent meta-analysis by Delewi et al.[30] revealed that intracoronary BMC treatment leads to a moderate improvement in LVEF and a reduction of left ventricular end-systolic volume (LVESV) at 6 months that sustained at 12 months follow-up, without a clear significant effect on left ventricular end-diastolic volume (LVEDV) or infarct size. The authors also found that intracoronary cell therapy was significantly associated with reductions in recurrent acute MI and readmission for HF, unstable angina, or chest pain.

Chronic Ischemic Heart Disease with Myocardial Dysfunction

Patients with chronic ischemic left ventricular dysfunction may have a substantial amount of viable hibernating myocardium, which is detected by multiple methods such as cardiac magnetic resonance; therefore, coronary revascularization in these patients may result in an improvement of left ventricular function (Table 2). Moreover, the effect of the addition of BMCs by intracoronary or intramyocardial injection on these results has been tested in a few studies.[31-33] Zhang et al.[34] performed a meta-analysis of 11 clinical trials that evaluated the efficacy of autologous BMC transfer in 490 total patients with chronic ischemic heart disease. Compared with controls, BMC-treated patients significantly improved LVEF by 4.63% and showed a significant reduction in LVEDV and LVESV. In addition, BMC treatment was associated with a significant positive effect on survival. The authors suggest that in this subgroup of patients, BMC transfer seems to have a positive impact on myocardial remodeling, unlike patients treated in the acute phase, or within 1 week, of MI.

Strauer et al.[35-36] have recently reported long-term follow-up data on the intracoronary application of BMC in patients with chronic HF due to ischemic CM (LVEF <35%) from the nonrandomized STAR study. Throughout a 5-year follow-up, the authors reported improved LVEF, quality of life, and survival in patients with HF who received BMC (191 patients with mean NYHA class 3.22) compared to the control group (200 patients) with a similar LVEF.

Study	No. of Patients	LVEF (%) Baseline	Follow-up (Months)	Cell Type	Delivery Route	LVEF Increase (%)
ASTAMI (2006)	100	46	6	BMC	IC	No effect
FINCELL (2008)	80	58.8	6	BMC	IC	7.1
REGENT (2009)	200	36	6	BM-MNC / CD 34+ / CXCR4+	IC	No effect
BOOST (2009)	60	51	6	BMC	IC	6.7
BONAMI (2010)	101	36.3	3	BMC	IC	No Effect
REPAIR-AMI (2010)	204	45.4	24	BMC	IC	4.7
HEBE (2011)	200	38.6	4	BMC	IC	No Effect
TOPCARE (2011)	59	46	60	CPC / BMC	IC	11
Late Time (2011)	87	48.7	6	BM-MNC	IC	No Effect

Table 1. Prospective randomized trials of stem cell therapy in acute myocardial infarction. LVEF: left ventricular ejection fraction; BMC: bone marrow-derived cells; BM-MNC: bone marrow-derived unselected mononuclear cells; CPC: circulating progenitor cells; IC: intracoronary.

Study	No. of Patients	LVEF (%) Baseline	Follow-up (Months)	Cell Type	Delivery Route	LVEF Increase (%)
REPAIR-AMI (2006)	204	48	12	BMC	IC	2.5
TOPCARE-CHD (2006)	121	40	12	BMC	IC	1.8
STAR-heart (2010)	391	33	24	BMC	IC	6.2
FocusHF (2011)	30	37	6	BM-MNC	IM	No Effect
SCIPO (2011)	14	30	4	CDC	IC	8.2
CADUCEUS (2012)	25	39	6	CDC	IC	No Effect
Sürder et all.[28] (2013)	200	37.4	4	BM-MNC	IC	No Effect

Table 2. Prospective randomized trials of stem cell therapy in ischemic heart failure. LVEF: left ventricular ejection fraction; BMC: bone marrow-derived cells; BM-MNC: bone marrow-derived unselected mononuclear cells; CDC: cardiosphere-derived cells; IC: intracoronary; IM: intramyocardial.

Nonischemic Dilated Cardiomyopathy

There is little evidence of the potential benefit of cell therapies in nonischemic etiologies, as some patients exhibit nonhomogeneous tissue perfusion on nuclear imaging, which is the basis of target-area selection for stem cell administration. The studies performed have shown that BMC administration attenuates the effects of circulating autoantibodies, which are thought to be involved in the pathogenesis of nonischemic dilated CM (Table 3). In the study by Vrtovec et al.,[37] 55 patients were randomized to intracoronary infusion transplant of CD34 + progenitor cells or placebo. At 1 year, cell therapy resulted in significant improvement in LVEF (25.5% ± 7.5% to 30.1% ± 6.7%, P = .03), an increase in the 6-minutes walk distance (359 ± 104 m to 485 ± 127 m, P = 0.001), and a decrease of NT-proBNP levels (2069 ± 1996 pg/mL to 1037 ± 950 pg/mL, P = 0.01); cell therapy was the only independent prognostic factor to remain free of death or cardiac transplantation (2/28, 7% to 8/27, 30%, P = .03). The 5-year follow-up, in addition to demonstrating the middle-term safety of the procedure, also showed a persistent improvement in LVEF and exercise capacity, maintaining the benefit of reduced mortality from HF.[38]

Seth et al.[39] analyzed a cohort of 44 patients with nonischemic HF, comparing 20 controls to 24 who were randomized to cell therapy using intracoronary infusion of bone marrow-derived mononuclear cells. There was a significant improvement in NYHA functional class in the treatment group, with 16 patients (62%) who improved by at least one degree of functional class. In addition, ejection fraction improved by 5.4% (20 ± 7.4% to 25 ± 12%, P <0.05) with no change in left ventricular end-diastolic volume. The 3-year follow-up showed persistent improvement in LVEF, mainly by decreases in left ventricular end-systolic volume without changes in end-diastolic volume. It also showed an improvement in functional class (although less pronounced in NYHA class IV) and improvement in quality of life, although it did not demonstrate improved survival.[39]

Fischer et al.[40] performed intracoronary infusion of bone marrow-derived cells on 33 patients with dilated nonischemic cardiomyopathy and analyzed hemodynamics and cardiac function by Doppler at 3 months. There was an improvement in global and segmental contractility, with a significant increase in LVEF (30.2% ± 10.9% to 33.4% ± 11.5%, P = .001). Dynamics showed a lower coronary vascular resistance index unchanged in the reference vessel diameter, which could result in improved micro- and macrovascular endothelial function; they also showed a significant decrease at 1 year in NT-proBNP levels (1610 ± 993 to 1473 ± 1147 pg/mL, P = 0.038), a known neuroimmunomodulator with well-established prognostic implications in patients with HF.[40]

Study	No. of Patients	LVEF (%) Baseline	Follow-up (Months)	Cell Type	Delivery Route	LVEF Increase (%)
Bocchi et al.[49] (2008)	22	21	15	BMC	IC	8.8
Fischer-Rasokat et al.[40] (2009)	33	30	3	BMC	IC	3.4
Seth et al.[39] (2010)	85	23	36	BMC	IC	5.9
Vrtovec et al.[37] (2011)	55	26	12	Autologous CD 34+	IC	4.6
Vrtovec et al.[38] (2013)	55	24	60	Autologous CD 34+	IC	5.6

Table 3. Prospective randomized trials of stem cell therapy in nonischemic heart failure. LVEF: left ventricular ejection fraction; BMC: bone marrow cells; IC: intracoronary.

Inflammatory Paracrine Response to Stem Cell Therapy

Several studies have focused on the ability of stem cells to improve or regenerate myocardium by injecting cell suspensions containing either mixed or purified cellular population into the heart. Despite the apparent benefit of this experimental procedure, the mechanisms remain controversial and unclear, leaving large gaps in the understanding of the actual outcome of stem cell therapies and its future implications in the field of medicine. Few reports have focused on the immunologic aspects of the inflammatory paracrine response to stem cell therapy that might lead to improved cardiac function, cell proliferation, angiogenesis, or vasculogenesis by secreted chemical mediators via inflammatory cell infiltration and immunologic reactions.

Preclinical models have confirmed the main role of paracrine effects as part of stem cell therapy benefits, demonstrating attenuated apoptosis of endothelial cells and cardiomyocytes[41] as well as cardiac function improvement[42] and tissue perfusion related to angiogenesis and arteriogenesis.[43] These effects are apparently significantly related to lymphohistiocytic infiltration at stem cell injection sites.[44] The importance of monocytes and macrophages in myocardial tissue healing and prevention of ventricular remodeling has been tested in several models[45-46] and has shown that macrophages act as producing factors that protect hypoxic cardiac cells from apoptosis.[47]

Some authors suggest that the beneficial action of stem cells depends on their ability to recruit lymphohistiocytic compounds more than on cell differentiation to new cardiomyocytes, and that the most important positive effects are related to the death of implanted cells in the site of transplantation rather than the intact stem cells by themselves (Figure 2).[48] This hypothesis could be well established by clinical trials that have shown how intracoronary stem cell transplantation can lead to improved ventricular remodeling and function, exercise tolerance, and long-term survival in patients with initial higher intramyocardial homing, despite low cell retention at the end of the study.[37-38] One of the main factors affecting the efficacy of stem cell therapies seems to be the number of viable cells that achieve nesting on the affected myocardium. All cell subtypes may have different regenerative properties insofar as they tolerate adverse ischemic environments and interact with chemoreceptor expression; therefore, any measure to improve homing could have a significant impact on the effectiveness of cell therapy. Several techniques are currently being studied to better support cells, including multicellular therapy, modification of cell properties prior to infusion, increasing myocardial chemokine expression by electroshock, transport polymers, and tissue engineering gel.[49-52]

Conclusion

Stem cell regenerative cardiac therapy appears to be a safe treatment modality for patients with ischemic and nonischemic cardiac disease, mainly promoting neovascularization and improving endothelial dysfunction. The results of meta-analysis addressing the clinical applicability suggest middle- and long-term improvement in cardiac function, specifically LVEF, exercise tolerance, functional class, quality of life, and scar size; however, the effect on adverse remodeling processes is less clear. Several important aspects need to be addressed, namely discriminating cell populations, dosing, timing, homing modulation, and delivery routes. Clarification of these issues may translate into better outcomes for patients. Further studies are needed to define the underlying mechanisms of stem cell therapy response and develop methods to further improve stem cell homing and survival.

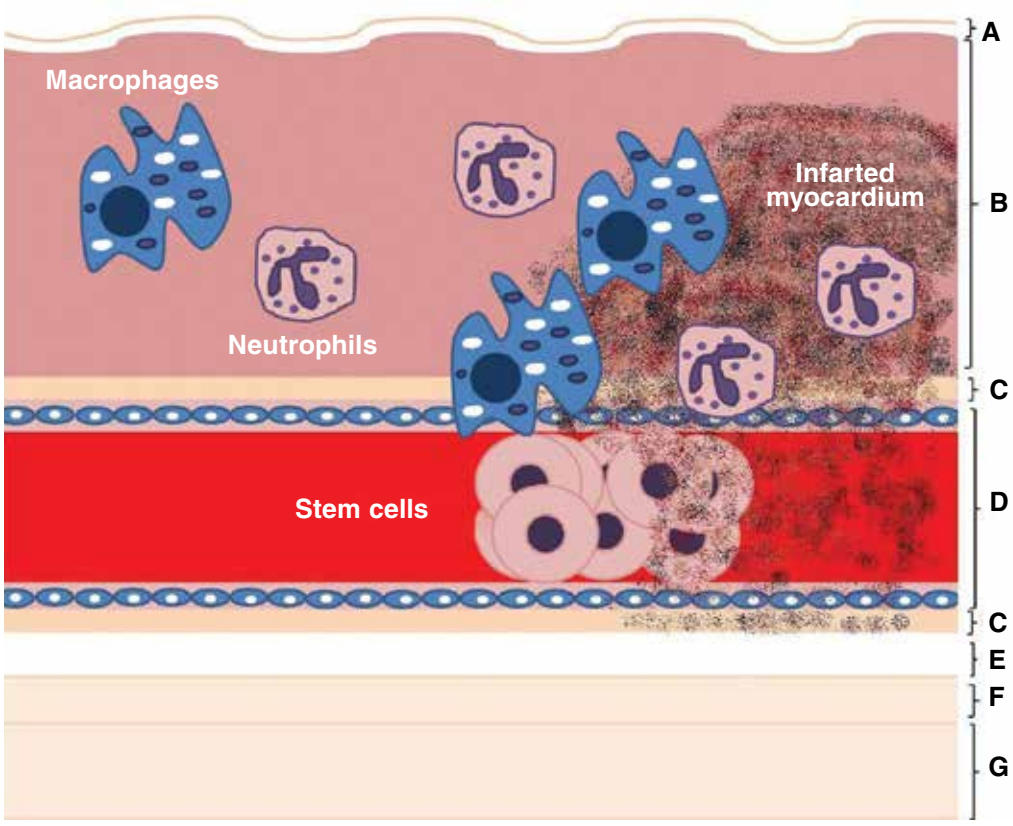

Figure 2. Inflammatory paracrine response to stem cell therapy. The presence of neutrophils and macrophages on myocardial tissue (lymphohistiocytic infiltration) heals and prevents ventricular remodeling at stem cell injection sites. (A) Endocardium; (B) Myocardium; (C) Epicardium; (D) Coronary blood vessel; (E) Pericardial cavity; (F) Parietal pericardium; (G) Fibrous pericardium.

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Keywords: heart failure, cardiac stem cell therapy, bone marrow-derived cell therapy, dilated cardiomyopathy

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