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Stem cell use for cardiac diseases as of 2008

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Abstract

Congestive heart failure and coronary artery disease are the leading causes of morbidity and mortality in the western society despite substantial therapeutic advances in the last half century. Only very recently have studies arisen that support possibility of regenerating tissue of damaged human organs including the heart. In this regard, there is growing preclinical and clinical evidence demonstrating the safety and efficacy of cell-based myocardial regeneration using a variety of cell lines. Different mechanisms have been proposed to explain the beneficial effects of cell-based therapy. The beneficial effects of cell therapy may involve multiple mechanisms. The encouraging results of early clinical cell therapy studies have not been sustained by subsequent robust studies for all cell types. These findings suggest that many unanswered questions need to be addressed before cell therapy becomes an acceptable adjunctive treatment for heart disease. Future setbacks are likely, but both clinicians and basic scientists will eventually introduce more potent cell-based strategies into the clinical arena.

Keywords: Heart failure; Embryonic stem cells; Myoblasts; Bone marrow-derived mononuclear cells; G-CSF

1. Introduction

In attempting to achieve cardiac cell-based replacement therapy, a variety of cells have been contemplated, and there is emerging preclinical and clinical data on the efficacy and safety of different cell lines in the setting of acute myocardial infarction and chronic heart failure including embryonic stem cells (ESCs), skeletal myoblasts, bone marrow mononuclear cells (BMC), circulating progenitor cells such as endothelial progenitor cells, mesenchymal cells, and cardiac stem cells. The clinical trials that have been performed in patients with myocardial infarction and chronic heart failure document improved systolic function after administration of stem cells, translating their regenerative potential from the bench to the bedside. In this review series, the existing preclinical and clinical data supporting the use of various cellular preparations and the suggested mechanisms of action will be discussed in further details.

2. Embryonic stem cells

Embryonic stem cells (ESCs) are conceived as a highly promising therapeutic approach because they are totipotent. In this regard, they are characterized

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by their capacity to proliferate in an undifferentiated state while maintaining their capacity to differentiate into cell lines from all 3 embryonic germ layers. Human ESCs when cultivated in suspension form contracting areas, embryoid bodies, which are positive for cardiomyocyte markers such as myosin heavy chain, α-actinin, desmin, and troponin I [1]. Embryonic stem cells are capable of differentiating into cardiomyocytes with the capacity to propagate action potentials, as well as endothelial and smooth muscle cells [1–3]. Administration of ESCs in an animal model of myocardial infarction results in engraftment, improved left venticular (LV) function and reduced LV remodelling [4,5].

Embryonic stem cells have obvious important limitations as a therapeutic agent given their propensity toward teratoma formation, immunogenecity, and the ethical issues raised by their use [6]. Indeed, the greatest value of ESCs currently is it being a model system for development, but indeed they hold substantial promise as a potential therapeutic agent.

3. Skeletal myoblasts

In the quest to develop adult cell-based therapies, both skeletal myoblasts and bone marrow-derived cells have been studied in detail at mechanistic, translational, and clinical levels. Based on the concept that they could possess plasticity sufficient to give rise to cardiac muscle, skeletal myoblasts obtained from skeletal muscle biopsies were among the earliest cell types used for cardiac regeneration. Among their postulated advantages are the ability to derive autologous cells, thereby eliminating the need for immunosuppression [7]. In addition, skeletal myoblasts have high proliferative capacity at a later stage of differentiation and are resistant to ischemia [7,8]. These cells are committed to a myogenic lineage and as such are less teratogenic than ESCs. Preclinical and clinical studies of post-myocardial infarction (post-MI) administration of skeletal myoblasts demonstrate engraftment and functional improvement [8–10]. However, engrafted myoblasts have not proven to differentiate into cardiac myocytes, leading to the idea that the beneficial effects of their administration derive from paracrine effects, autonomous contraction, infarct size reduction, or alteration in mechanical properties of the scar [11]. Myoblasts secrete a variety of angiogeneic and antiapoptotic factors similar to paracrine factors released from the bone marrow [12,13]. A variety of clinical studies have assessed safety and efficacy of skeletal myoblasts using both intracoronary and intramyocardial modes of delivery in patients with chronic ischemic cardiomyopathy [14–18]. Inability of skeletal myoblasts to transdifferentiate to cardiomyocytes and to form electrical junctions has raised potential concerns regarding formation of substrate for ventricular reentry tachycardia [15,18].

The results of the MAGIC trial presented by the principal investigator Prof. Menache at the 4th International Symposium on Stem Cell Therapy and Applied Cardiovascular Biology (Madrid, Spain, April 26th–27th 2007) are very interesting in context of safety and efficacy [19]. The MAGIC trial is a multicenter, randomized, placebo-controlled, double-blind 3-arm trial including patients with left ventricular (LV) dysfunction (ejection fraction <35%) and indication for coronary artery bypass surgery. Each patient received either cells (400 or 800 million) grown from a skeletal muscle biopsy for 3 weeks or a placebo solution injected into 30 sites in and around the scar. An internal cardioverter-defibrillator was implanted in all patients before hospital discharge. The 6-month safety endpoints comprised a composite index of major cardiac adverse events (MACE) and ventricular arrhythmias [19]. The co-primary efficacy end points were changes in global and regional LV function assessed by echocardiography. Ninety-seven patients received injections of myoblasts (400 million; $n = 33$; 800 million; $n = 34$) or placebo ($n = 30$). The time-to-first MACE and the time-to-first arrhythmia did not differ significantly between the 3 groups. Myoblast transfer did not improve regional or global LV function beyond that seen in control patients. Interestingly, however, the high dose cell group demonstrated a significant decrease in LV enddiastolic and endsystolic volumes compared with the placebo group [19]. In a subgroup of 48 patients who underwent an additional functional assessment by nuclear angiography, ejection fraction was significantly increased in those injected with the high cell dose of cells compared with the placebo group. Myoblast injections as an adjunct to coronary surgery in patients with ischemic cardiomyopathy and depressed LV function look safe but failed to further improve echocardiographic heart function at 6 months follow-up. However, the significant reversal of LV remodelling following high dose myoblast injections provides additional proof of concept for cardiac cell therapy [19]. The results of this landmark trial give us important clinical insights