Stem Cell Therapy for Heart Failure

Amit N. Patel, MD, MS*, Francisco Silva, MS, Amalia A. Winters, BSc

KEYWORDS

• Stem cell • Delivery • Heart failure • Clinical trials

KEY POINTS

- During the past decade, studies in animals and humans have suggested that cell therapy has positive effects for the treatment of heart failure.
- This clinical effect may be mediated by angiogenesis and reduction in fibrosis rather than by regeneration of myocytes.
- Increased microvasculature and decreased scar also likely lead to improved cardiac function in the failing heart.
- The effects of cell therapy are not limited to one type of cell or delivery technique.
- Well-designed, large-scale, randomized clinical trials with objective end points will help to fully realize the therapeutic potential of cell-based therapy for treating heart failure.

STEM CELL THERAPY FOR HEART FAILURE

Heart failure (HF) is the inability of the heart to pump sufficient blood to meet the body's oxygen demands. It is classified as ischemic (cause by atherosclerosis, decreased perfusion, or myocardial infarction) or nonischemic (caused by viral infection or congenital or idiopathic disease). Regardless of the cause, congestive HF is the final common pathway, marked by cardiomyocyte death, inflammation, and scar formation resulting in loss of contractility. Despite significant therapeutic advances, the prognosis for patients hospitalized with HF remains poor, with a 5-year mortality of approximately 50%. Additionally, HF creates a heavy burden on health care resources.

HF therapies improve symptoms and can prolong life, but are unable to replace scar tissue or awaken hibernating myocardium via angiogenesis. Currently, cell-based technology is emerging as a novel therapy with the potential to dramatically transform the treatment of HF through inducing myocardial repair and regeneration.

Efficient delivery of cells to the target site is critical for effective clinical outcomes. Cell therapy may be delivered to the heart through several routes: direct injection into the myocardium via endocardial or epicardial approaches, coronary artery infusion, intravenous infusion, epicardial patch, or retrograde coronary sinus infusion.

This article discusses the use and delivery techniques of various stem cell-based therapeutics for the treatment of HF, along with advances, challenges, and future directions.

EPIDEMIOLOGY, PATHOPHYSIOLOGY, AND TREATMENT OF HEART FAILURE

HF is a common, lethal, and expensive disorder. It is one of the most common causes of hospitalization in industrialized countries, and the incidence is increasing with concomitant increases of morbidity, mortality, and consumption of health care resources. Although ischemic and nonischemic heart disease contribute to a final common pathway marked by a cycle of inflammatory

University of Utah School of Medicine, 30 North 1900 East 3c127 SOM, Salt Lake City, UT 84132, USA
* Corresponding author. University of Utah School of Medicine, 30 North 1900 East 3c127 SOM, Salt Lake City, UT 84132.
E-mail address: amit.patel@hsc.utah.edu

Heart Failure Clin 11 (2015) 275–286
http://dx.doi.org/10.1016/j.hfc.2014.12.006
1551-7136/15/$ – see front matter

mediator release, cardiomyocyte death, and scar formation, leading to HF, development of novel therapies requires an understanding of the different pathophysiology of these causes.[1–3]

Pathophysiology of Ischemic Heart Failure

Ischemic HF is the end result of insufficient blood flow to the myocardium caused by occlusive disease of the coronary arteries. Atherosclerosis narrows the arterial lumen and leads to decreased myocardial oxygen delivery, with both chronic and acute effects. Narrowed, calcified coronary arteries cannot accommodate the increased blood flow required in the setting of increased oxygen demand (eg, exercise). A myocardial infarction occurs when myocardium distal to the arterial blockage receives no blood flow and subsequently dies. Infarcted myocardium is replaced by fibrotic tissue that does not have the same contractile properties as healthy heart muscle, resulting in a heart that functions abnormally. The fraction of myocardium replaced with fibrosis is a predictor of all-cause mortality and adverse cardiovascular events in patients with HF.[4] If the areas of ischemia are large enough, valvular integrity and contractile function can be compromised and HF can develop. Current treatments focus on improving blood flow through these major arteries using angioplasty or stenting, or providing a new source of blood flow to an ischemic region, such as through coronary artery bypass grafting.

Pathophysiology of Nonischemic Heart Failure

Nonischemic HF is a disease characterized by microvascular dysfunction. The major coronary arteries remain patent, but the disease is marked by decreased capillary density, increased microvascular resistance, and insufficient vasodilation of the small myocardial vessels in response to increased oxygen demand. Patients demonstrate reduced myocardial blood flow even at rest.[5] This "blunted perfusion reserve" in the setting of normal coronary arteries is the main feature of nonischemic HF.[6] Microvascular dysfunction sets the stage for recurrent, frequent episodes of myocardial ischemia. This condition ultimately leads to ventricular wall thinning and global cardiac dysfunction marked by pump failure and arrhythmias.[7] The degree of microcirculatory dysfunction is an independent predictor of mortality. It is important to note that coronary microvascular dysfunction is not an effect of myocardial damage but rather is the cause of the ischemic substrate that results in progressive myocardial injury and HF. In nonischemic HF, the pattern of myocardial injury is more diffuse than in ischemic disease. This global dysfunction means that treatments for nonischemic HF are limited to inotropic medications or ventricular-assist devices (neither of which stop or reverse HF), or cardiac transplantation. An intervention targeted at improving microvascular function in nonischemic cardiomyopathy may improve outcomes in HF or prevent patients from progressing to failure.

CELL OPTIONS FOR THE TREATMENT FOR HEART FAILURE

This article discusses the source of stem cells and routes of delivery along with their safety and efficacy for the treatment of HF. Clinical trials that have been registered with ClinicalTrials.gov are mentioned, along with their assigned numbers.

Skeletal Myoblasts

Skeletal myoblasts are progenitor cells derived from skeletal muscle. They were the first cells to be tested in both preclinical and clinical studies for HF.[8–11] Although early clinical studies reported engraftment and significant improvement in cardiac function, subsequent clinical studies, including a 97-patient phase II randomized, placebo-controlled, double-blind trial, failed to reproduce these results.[9] In several patients, ventricular tachyarrhythmias were noted after cell transplantation. With poor clinical outcomes and the potential for increased adverse events, skeletal myoblasts have a limited role in cell-based therapy for HF.

Peripheral Blood Cells

Peripheral blood–selected CD34+ cells have been used in the treatment of patients with ischemic HF with promising results.[12] The issues related to using granulocyte colony-stimulating factors for peripheral blood mobilization, apheresis, and the costs associated with CD34+ selection have limited the use of this cell product. The long-term benefits of using blood-selected cells in patients with acute myocardial infarction have been shown to be less favorable compared with using bone marrow cells.[13] This finding has further limited the use of peripheral blood for treating ischemic heart disease. However, this technique still has potential benefit, which is currently being evaluated (ClinicalTrials.gov identifier: NCT01350310).[14] The mechanism of possible benefit for peripheral blood CD34+ cells in patients with nonischemic versus ischemic HF has not been identified.

Bone Marrow Mononuclear Cells

Bone marrow mononuclear cells (BMMNCs) are a heterogeneous cell population composed of