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Review Article

Cellular therapies for chronic ischemic heart failure

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ABSTRACT

The development of stem cell therapies for chronic ischemic heart failure is highly sought after to attempt to improve morbidity and mortality of this prevalent disease. This article reviews clinical trials that investigate stem cell therapy for chronic ischemic heart failure. To generate this review article, PubMed was searched using keywords “stem cell therapy heart failure” with the article type “Clinical Trial” selected on 10/04/2016. The raw search yielded 156 articles; 53 articles were selected for inclusion in the review between the original literature search and manual research/cross-referencing. Additional reviews and original articles were also manually researched and cross-referenced. Cellular-based therapies utilizing peripheral blood progenitor cells, bone marrow cells, mesenchymal stem cells, cells of cardiac origin, and embryonic stem cells have yielded mixed results, but some studies have shown modest efficacy. Skeletal myoblasts raised concerns about safety due to arrhythmias. Optimizing cell type and delivery method will be of critical importance in enhancing efficacy of therapy within various subsets of chronic ischemic heart failure patients. Although much more work needs to be done to optimize treatment strategies, developing stem cell therapies for chronic ischemic heart failure could be of critical importance to lessen the impactful health burden that heart failure has on patients and society.

1. Introduction

Cardiovascular disease is the number one cause of death in the United States.[1] As the U.S. population ages and treatments continue to improve so that patients survive initial cardiac events such as myocardial infarctions, the number of individuals suffering from ischemic heart failure will increase. Despite some advancement in medical treatment regimens, morbidity and mortality remain strikingly high upon onset of symptomatic heart failure, and there is difficulty in predicting prognosis in individual patients.[2-10] As such, next-generation therapies need to continue to be developed. This review discusses clinical trials of stem-cell therapies for chronic ischemic heart failure. It is organized based on the origin of the cellular therapies: peripheral blood progenitor cells, bone marrow cells, a more in-depth look at mesenchymal stem cells (MSCs) (which can come from multiple sources), skeletal myoblasts, cells of cardiac origin, and embryonic stem cells. This review summarizes clinical trials investigating peripheral blood progenitor cells, bone marrow cells, MSCs (which can come from multiple sources), skeletal myoblasts, cells of cardiac origin, and embryonic stem cells for chronic ischemic heart failure treatment.

2. Methods

PubMed was searched using keywords “stem cell therapy heart failure” with the article type “Clinical Trial” selected on 10/04/2016. The raw search yielded 156 articles; 99 articles were selected on the basis of abstract review for further abstract and full text review because of their focus on clinical trials involving stem cell therapies in heart failure; 53 articles were selected for inclusion in the review from a pool of the original literature search plus manual research/cross-referencing because they described clinical trials with stem cell therapies in patients with chronic ischemic heart failure (or studies that included both chronic ischemic and non-ischemic heart failure patients). Additional reviews and original articles

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were also manually researched and cross-referenced to include a more complete description of clinical trials, preclinical work, and reviews of the field. An outline of the literature search and selection is shown Fig. 1. Table 1 shows a summary of the main clinical trials covered in this review.

3. Peripheral Blood Progenitor Cells

The peripheral blood can serve as an easily accessible source of stem cells. Granulocyte colony-stimulating factor (G-CSF) is a cytokine that causes the bone marrow to produce stem cells and release them into the peripheral blood. G-CSF treatment to increase the number of CD34+ cells (hematopoietic stem cells [HSCs]) or endothelial progenitor cells (which are derived from HSCs) in the peripheral blood did not induce myocardial infarction, congestive heart failure, or death in a small phase 1 study but did increase the intensity and/or frequency of angina, bone pain, headache, and hospitalization during mobilization.[11] In a preliminary study investigating patients with both ischemic and dilated cardiomyopathy, peripheral blood stem cells were harvested after stimulation with G-CSF and implanted by intramyocardial injection during thoracotomy.[12] Preoperatively, of the 27 patients who received follow-up, 26 patients had a functional class III based on the New York Heart Association (NYHA) classification, while postoperatively, 5 were class II and 15 were class I. The ejection fraction went from 37.7% ± 14.2% to 42.15% ± 5.9%.[12] However, two patients died from arrhythmias perioperatively, and seven had incidence of ventricular fibrillation during the procedure that required defibrillation.[12] In a prospective crossover study, when patients with ischemic heart failure were treated with transendocardial injected CD34+ cells from peripheral blood mobilized with G-CSF, they exhibited increased left ventricular ejection fraction from 27.1% ± 6.6% to 34.9% ± 10.9% (P = 0.001), improved 6-minute walking distance from 411 ± 116 m to 496 ± 113 m (P = 0.001), and improved N-terminal pro B-type natriuretic peptide levels (NT-proBNP) from 3672 ± 5165 pg/mL to 1488 ± 1847 pg/mL (P = 0.04).[13]

The TOPCARE-CHD trail investigated intracoronary delivery of circulating blood or bone marrow–derived progenitor cells in patients who had suffered a myocardial infarction 3 months ago or greater and had stable ischemic heart disease.[14] It consisted of three phases.[14] Phase 1 was a pilot trial where some patients received circulating blood or bone marrow–derived progenitor cells.[14] In phase 2, patients received no cellular infusion, circulating blood progenitor cells, or bone marrow–derived progenitor cells.[14] In phase 3, patients in the control group were randomly assigned to receive circulating blood progenitor cells or bone marrow–derived progenitor cells, and patients in the groups that initially received cellular infusions were crossed over to receive the other cell type.[14] There was a statistically significant +2.9% absolute change in the left ventricular ejection fraction in patients who received bone marrow–derived progenitor cells compared to those who received circulating blood progenitor cells (−0.4%, P = 0.003) or no infusion (−1.2%, P < 0.001).[14] Both global cardiac function and regional contractility were improved in the bone marrow–derived progenitor cells, and this was also observed in the crossover phase of the study when patients received bone marrow–derived progenitor cells irrespective of whether they were originally in the circulating blood progenitor cell or control group.[14]

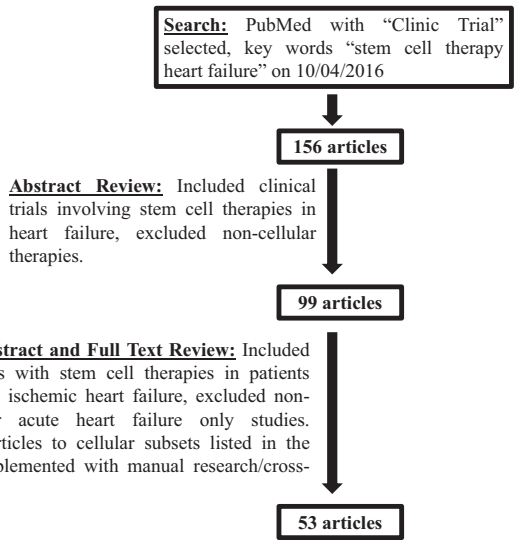

Fig. 1. Literature search and selection. Outline of the literature search and selection of clinical trials.

In a pilot study, patients who had refractory ischemic heart failure after a myocardial infarction received one dose of G-CSF and multiple intracoronary deliveries of peripheral blood stem cells, one dose of G-CSF and one dose of peripheral blood stem cells, or neither.[15] At 1-year follow-up, patients who received multiple peripheral blood stem cell treatments had left ventricular ejection fractions statistically significantly higher (47.00±4.90%) than those who received a single cell treatment (44.40% ± 3.87%, P < 0.01) or no cell treatment (40.80% ± 3.41%, P < 0.01), and myocardial perfusion was improved more in patients who received multiple cell treatments than those who received one (P = 0.012) or not any treatment (P < 0.01).[15]

Other strategies to harvest stem cells from the peripheral blood have also been used. Peripheral blood multipotent progenitor cells rich in CD45, $CD31^{Bright}$, $CD34^{+}CD45^{-/Dim}$, and $CD34^{Bright}$ cells were collected, cultured with vascular endothelial growth factor (a growth factor that helps stimulate vasculogenesis and angiogenesis), and resulting cells phenotypically characterized and injected into patients with dilated or ischemic cardiomyopathy.[16] In patients with ischemic cardiomyopathy, the ejection fraction went from 26.6% ± 5.8% to 33.6% ± 7.8%.[16] In looking specifically at CD133+ endothelial progenitor cells (cells of HSC lineage), after G-CSF stimulation, autologous peripheral blood CD133+ endothelial progenitor cells were delivered to the infarcted region by percutaneous angiography in 7 patients with chronic post-infarct cardiac insufficiency, of which 2 died after observation from noncardiac conditions.[17] However, the remaining 5 patients had improvements in their NYHA classification, had no hospital admissions for heart failure, and had an improved ejection fraction from 35% to 40% observed by echocardiography (P = 0.013) and cardiac MRI (P = 0.009) 24 months post-treatment.[17] Without using a mobilization strategy, autologous CD34+ cells obtained from peripheral blood were delivered by transcoronary transplantation in 7 patients in the chronic phase after myocardial infarction, and a statistically significant decrease in end-systolic volume was observed after treatment (P<0.03).[18]

In general, older age reduces peripheral blood CD34+ cell concentrations and reduces the effects of G-CSF on bone marrow stem cell mobilization in ischemic heart disease patients.[19] Ischemic heart disease patients have lower levels of peripheral blood CD34+ and endothelial progenitor cells compared to dilated cardiomyopathy patients.[19] G-CSF treatment more dramatically increases bone marrow compared to peripheral blood CD34+ concentrations, but the peripheral blood CD34+ cells appear to have a higher functional potential compared to baseline and more work will have to be done to determine which is a better source of stem cells.[19] Overall, peripheral blood progenitor cells

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