

REVIEWS

Cardiac Stem Cell-Derived Treatment for Ischemic Heart Disease: A Review

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Keywords: cardiac stem cells, ischemic heart disease

<https://doi.org/10.52504/001c.87728>

Georgetown Medical Review

Vol. 7, Issue 1, 2023

Current first-line pharmacologic therapies for ischemic heart disease (ISD) have proven largely ineffective, leading to the exploration of alternative treatments. Various stem cell-like/progenitor cell lineages have been studied, especially c-kit+ cardiac stem cells (CSCs) due to their true stem cell origin and differentiation capabilities. These CSCs reside in the heart after birth and possess regenerative potential, providing a means of maintaining and repairing myocardial tissue. Previous studies have demonstrated the therapeutic potential of CSCs for patients with ISD. However, counterarguments have focused on the inflammatory state present in diseased hearts, which may limit the benefits of c-kit+ CSCs. Nonetheless, we argue that a thorough examination of the literature supports the potential of c-kit+ CSCs as a safe and effective therapeutic approach for restoring lost cardiac tissue and function in patients with ISD. Though promising, we believe further scientific inquiry is necessary to discern the exact mechanisms by which c-kit+ CSCs function, which could pay dividends in the approach to treating ISD.

Introduction

Until the early 2000s, it was understood that the heart is a largely nonregenerative structure in the body.¹ Following myocardial infarction, the loss of the number of cardiomyocytes and subsequent loss of function can lead to ischemic cardiomyopathies and heart failure, which are 2 significant causes of morbidity and mortality.² Patients with this sequelae of ischemic injury have been limited in their options to regain cardiovascular health and function, left with only compensatory pharmaceuticals, surgical intervention, or device placement as options for treatment.¹ Although these therapies are the current standard of care, they are inadequate in addressing the primary insult of cardiomyocyte loss that leads to the severely limiting and often fatal conditions that can follow ischemic injury of the heart, such as cardiac arrhythmia and heart failure.¹ Until the emergence of stem cells, the only available therapy to treat end stages of cardiomyopathy and heart failure was to address the underlying cause, the loss of cardiomyocytes, via heart transplant.¹ Although effective, this method is severely restricted by the limited number of donors as well as complications of heart transplants leading to poor long-term outcomes.^{2,3} In the past decade, stem cells have emerged as novel, less-invasive agents to replace damaged heart tissue and regain cardiomyocyte function, preventing the deterioration into conditions that can severely decrease quality of life and even be fatal.² Since the revelation that the heart is, in fact, able to regenerate, much research has gone into exploring which lineage of cardiac cells is responsible. Numerous cell types within the adult heart have been

identified as having stem cell–like abilities, but further evaluation is necessary to determine whether these cells are truly stem cells as opposed to progenitor cells and the significance this imposes on the types of tissue they are able to repopulate.⁴ The fate map of each cell type is also relevant in determining its capability to not only restore myocardium, but also myocardial function.

There are 3 main protein markers used to delineate cardiac stem cells (CSCs): c-kit, Sca-1 (stem cells antigen–1), and islet-1.³ Among these, c-kit is most commonly used because c-kit+ cells are able to differentiate into cardiomyocytes, endothelial cells, and arteriole and capillary cells.³ Recently, there has also been a growing interest specifically in the use of CSCs that reside in the heart (resident CSCs) as opposed to other stem cell/progenitor–like cardiac cells from a safety perspective due to their lack of immunogenicity and cardioprotective benefits.¹

The purpose of this review was to examine the mechanisms and benefits of adult c-kit+ CSCs comprehensively, with a particular focus on their therapeutic outcomes in individuals with different cardiac diseases. We begin by discussing the working mechanism of CSCs and then proceed to analyze the benefits of CSCs, both alone and in combination with other types of stem cells, using randomized clinical trial analysis. Last, we explore potential shortcomings or adverse events associated with the use of adult CSCs, aiming to gain a better understanding of their safety and efficacy. From our analysis, the data have shown that the use of adult c-kit+ CSCs in the treatment of ischemic heart disease is uniquely both safe and effective in restoring cardiomyocyte population and function, especially compared with alternatives such as cardiospheres.

Cell Population Options for CSC Transplantation

Since the revelation that the heart is capable of regeneration, numerous studies have been done to further characterize the different populations of cardiac stem cells present within the heart itself.^{4–7} The most well-understood type of cells has been the c-kit+/Lin- population, which likely contains both true stem cells, those capable of differentiating into any cell type, and progenitor cells committed to the cardiac cell lineage.^{5,6} Focusing on the stem cell population, studies have confirmed that c-kit+/Lin- have the capacity to proliferate into cardiomyocytes, smooth muscle, and endothelial cells in vitro, but did not have the function and morphology of mature cardiomyocytes.^{5,6} However, studying c-kit+/Lin- in vivo via intracoronary injection into an ischemic heart showed more promising results in which the c-kit+/Lin- cells differentiated into new vessels and myocytes that were functionally able to reconstitute the previously injured myocardium.^{5,7}

However, it would be remiss not to address other resident cardiac stem and progenitor cell populations discovered that are also able to assist in cardiomyocyte repair and maintenance. The other 2 types of these non–c-kit+

cells include those expressing a stem cell antigen Sca-1 and progenitor cells derived from epicardium, identified based on their expression of Wt1. Both of these groups exhibit characteristics specifically of CSCs; however, their identity as a stem cell or progenitor cell and their efficacy in repairing myocardial injury has remained contested.⁵ Wt1 cells have been shown to increase cardiomyocyte generation, but additional studies on this cell type have shown more growth of vasculature rather than myocardium.^{4,8}

Furthermore, the distinction of origin amongst Sca-1+, alternatively called Isl1+, and c-kit+/Lin- cell types are necessary to understand how far along the differentiation pathway each cell group is because this determines their ability for repair and regeneration as well as the risk of tumorigenicity and other adverse effects of stem cell therapy. Subsequent studies further discerning the origins of these 3 cell types indicated that c-kit+ cells can be more accurately classified as stem cells because they are the most primitive progenitor cell type in murine models.⁵ Additionally, Sca-1+/Isl1+ cells are further committed to the myogenic differentiation pathway compared with c-kit+ cells, showing more cardiomyocyte-specific transcription factors, contractile proteins, ion channels, and calcium-binding proteins compared with c-kit+ CSCs.⁵

While the higher level of differentiation of Sca-1+ cells makes them an enticing stem cell therapy candidate because of the presumed decreased risk of tumorigenicity, the tradeoff is that recovery from myocardial injury requires cells that can differentiate into myocardium and other cell types for vascular restoration, the latter of which Sca-1+/Isl1+ cells may be unable to support in the adult heart. Another study has confirmed this, in which these cells were able to support myocardial, endocardial, endothelial, and smooth muscle growth in the embryonic heart, but were only able to reconstitute right atrium tissue in the adult heart.⁹ C-kit+ CSCs, however, have demonstrated to have the ability to differentiate into multiple cell types even in adult hearts. In addition, c-kit+ cardiac cells have been shown to have an origin independent of their bone marrow counterparts and separate from the Sca-1+/Isl1+ cell lineage, further supporting the identity of c-kit+ CSCs as true stem cells and possessing the qualities necessary for full cardiac regeneration and repair.⁵

Given the regenerative potential and confirmation of their independent identity as resident CSCs, specifically of c-kit+ CSCs, focus has shifted to characterizing the mechanism by which these cells are able to support myocardial repair. The earliest studies in 2005 indicated that c-kit+ CSCs play an endogenous maintenance role in the adult human heart because of its stem cell capabilities to differentiate into cardiomyocytes as well as endothelium and vascular smooth muscle.⁹ More recently, a study by Li et al³ in rat models also compared the treatment efficacy of c-kit+ CSCs vs that of c-kit- CSCs following myocardial infarction. Although both showed positive results, treatment with c-kit+ CSCs showed improved heart function recovery due to the additional benefits of increased angiogenesis and antiapoptotic effects

specific to c-kit⁺ CSCs.³ Earlier studies indicated that the sequelae of myocardial ischemia may be because this small resident population of CSCs responsible for maintenance has been overwhelmed by the size of tissue loss following ischemia and infarction.⁷ With promising results in animal models of c-kit⁺ CSCs to improve cardiac function following ischemic injury, additional studies have been pursued to demonstrate the advantages of CSCs in human hearts.⁴

Demonstrated Benefits of CSCs

Of interest is whether CSCs are a safe means to regenerate the function of damaged cardiomyocytes in humans given the promising results in murine and large-animal models. To this end, the potential benefits of CSCs for the regeneration of damaged heart tissue have been the subject of numerous clinical studies, many of which have demonstrated that CSCs are both safe and efficacious in ischemic conditions. While previous clinical trials using cardiosphere-derived cells and autologous and first-generation mesenchymal or bone marrow–derived stem cells yielded inconsistent results for ischemic heart conditions, CSCs have been found to have inherent advantages.¹⁰⁻¹² CSCs have powerful cardioprotective effects on the heart. Studies have demonstrated they promote angiogenesis, reduce scar formation, and activate the growth of new cardiac cells and vessels, contributing to the regeneration of damaged heart tissue.¹⁰

Sanz-Ruiz et al¹³ described the potential benefits of CSCs when outlining the rationale for the CAREMI trial, testing the use of allogeneic CSCs (AlloCSC-01) to restore cardiac structure and function after ischemic cardiovascular disease. Allogeneic CSCs may offer additional benefits because they can be derived from healthy donors and thus may have better regenerative potential than autologous cells, which may be affected by the patient's disease.^{10,13}

In a CAREMI trial follow-up study, Fernández-Avilés et al¹⁴ used intracoronary infusion to investigate whether CSCs could be used safely in patients with ST-segment elevation myocardial infarction and left ventricular dysfunction who were at high risk of developing chronic heart failure. The clinical trial enrolled 49 patients who were randomized to receive either allogeneic CSCs or a placebo. The authors established that CSCs could be safely used in the clinical setting because the infusion was well-tolerated at all dose levels and showed no immediate clinical, hemodynamic, or arrhythmic safety issues when compared with placebo. Additionally, no deaths, adverse events, or major adverse cardiac events occurred within the 30-day, 6-month, or 12-month intervals after treatment administration.¹⁴

The CAREMI trial was initially designed to test the safety, feasibility, and efficacy of early intracoronary delivery of allogeneic CSCs. Fernández-Avilés et al¹⁴ concluded that the study was not adequately powered to assess the

efficacy of treatment as demonstrated by CSC-mediated reduction in infarct size. However, their magnetic resonance imaging analysis showed a trend toward improvement in infarct size reduction in the group treated with allogeneic CSCs compared with the placebo group.¹⁴ Further analysis in adequately powered studies is needed to demonstrate whether allogeneic CSCs are effective at changing structural parameters in patients at an increased risk for adverse cardiac remodeling.¹⁴

In the SCIPIO trial,¹⁵ which studied the surgical delivery of autologous c-kit+ CSCs in patients with ischemic cardiomyopathy, the results confirmed that the administration of CSCs was safe and well-tolerated and provided further evidence of the efficacy of treatment with CSCs. The study included 16 patients who underwent coronary artery bypass grafting surgery and were randomized to receive standard therapy or an injection of CSCs in the area of the heart with the greatest damage from ischemic cardiomyopathy. Chugh et al¹⁵ demonstrated that patients who received CSCs had significantly improved left ventricular ejection fraction (LVEF) compared with the control group. This study showed that CSCs could be applied to improve cardiac function in an additional ischemic cardiac pathology.¹⁵

While the CAREMI and SCIPIO trials both used CSCs to treat an ischemic heart condition, they took vastly different approaches. There is growing evidence to support the use of less-invasive methods of delivering CSCs, such as intracoronary infusion, which was shown to be safe and feasible in the CAREMI trial as opposed to the more invasive surgical delivery of autologous CSCs in the SCIPIO trial.^{14,16} Additionally, combining CSCs with other stem cell therapies may offer even greater benefits in the treatment of ischemic heart conditions.

Combining CSCs With Other Stem Cell Therapies

Bolli et al¹⁶ conducted a double-blind, randomized, placebo-controlled trial known as the CONCERT-HF trial to assess the effects of intracoronary infusion of autologous mesenchymal stromal cells (MSCs) and c-kit+ CSCs, either alone or in combination, in patients with chronic ischemic heart failure. The study included 125 patients who were randomly assigned to receive MSCs, CSCs, both, or placebo. The results demonstrated that all treatments were safe, and there were no significant differences in adverse events between the treatment groups.¹⁶ However, in terms of efficacy, patients who received CSCs alone or both CSCs and MSCs had a significantly lower proportion of heart failure–related major adverse cardiac events compared with those who received placebo. The combination of MSCs and CSCs was associated with the best clinical outcomes in terms of heart failure–related major adverse cardiac events and quality of life. This suggests that intracoronary infusion of CSCs with or without MSCs may be a promising approach for reducing hospitalizations and improving the prognosis of patients with ischemic heart failure.

Of note and in further support of the specific advantages of c-kit+ CSCs as opposed to other populations of CSCs is the work by Makkar et al¹¹ in the CADUCEUS trial. The CADUCEUS study was a phase 1 trial exploring the efficacy of cardiosphere-derived autologous stem cells to reverse ventricular dysfunction following myocardial ischemia. Cardiospheres are groups of cells isolated from heart tissue containing an unknown ratio of c-kit stem cells and other cell types.⁴ These heterogeneous cell aggregates are thus capable of promoting angiogenesis and smooth muscle proliferation as well as cardiomyocyte regeneration, albeit in a less predictable or reproducible manner. Similar to the results from the aforementioned trials specifically of c-kit+ CSCs, cardiosphere-derived cells studied in the CADUCEUS trial merited a decrease in LV infarct size on magnetic resonance imaging at 1-year follow-up.¹¹ However, the trial did not show any improvement in LVEF, which has been confirmed to be a positive outcome in the c-kit+ CSC SCIPIO trial. In the SCIPIO trial, patients initially exhibited an EF of less than 40%. Of the 9 patients in the treatment group who were eligible to receive cardiac magnetic resonance imaging, 8 demonstrated an 8% improvement in EF 1 year after treatment that increased to 12% at 2 years.³ These results indicate that the benefits of treatment for LVEF were maintained and even increased over time. Furthermore, the SCIPIO and CAREMI trials on both autologous and allogeneic c-kit+ CSCs did not precipitate any major adverse cardiac events, whereas the CADUCEUS trial documented several adverse events within 12 months, including chest pain, acute myocardial infarction, and atrial fibrillation.^{11,14,16}

Thus, regarding the combination of c-kit+ CSCs with other cell types, we conclude that the promising results of CSCs, specifically combined with MSCs, merit further investigation. However, combination therapies, such as cardiospheres, which are a heterogeneous composition of the cell aggregates, are less reproducible and uniform across samples, which may make them more difficult to evaluate and later use as therapy.^{7,11}

Controversies in Current CSC Use

Although this review has thus far enumerated the benefits of c-kit+ CSCs, Many researchers have argued that the limitations and potential harms of using CSCs in a regenerative capacity outweigh any benefits they may offer. Alshammary et al¹⁷ noted that the effects of CSC transplantation may be heavily tied to the cell's original source; for instance, transplantation of skeletal myoblast predominates antifibrotic effects, while bone marrow–derived cell transplantation predominates neoangiogenesis.¹⁶ Thus, it can be reasoned that when exploring the application of CSCs to treat ischemic heart disease, there may be no one-size-fits-all cell line that can be reliably used in clinical scenarios with otherwise currently accepted treatments. Essentially, existing non–stem cell therapies may prove to be more efficacious depending on the source of the cell used and the condition being treated with it. Also, it could be difficult to show how these novel c-kit+ CSC treatments are superior to the current

standards of care. However, other studies have demonstrated that this drawback of “source limitation” may be overcome by adjusting the number and arrangements of cell layers used in the treatment.^{17,18}

Additionally, there is evidence to suggest that the application of c-kit+ CSCs may not be the best stem cell to use for the purpose of healing an ischemic heart after trauma. Koninckx et al¹⁹ noted that current treatment guidelines surrounding the use of c-kit+ CSCs is dependent on certain cell surface markers, which may be difficult to discern or are unreliable altogether because a plethora of cells on the human heart may express c-kit and additional resources would be needed to properly determine which of those are CSCs and thus suitable candidates for treatment.¹⁹ Instead, the authors noted that cardiac atrial appendage stem cells would be better for the treatment of ischemic heart disease due to their uniquely high expressions of aldehyde dehydrogenase compared with other CSCs.¹⁹ However, though the c-kit marker may be found within a variety of cell types within the heart, it is by far the most well-studied. Therefore, we believe it to be the best route for current treatment based on its demonstrated efficacy and general reliability across multiple studies, although more data are needed on other CSC types to assess their efficacies relative to one another.

Another class of concerns that exist for using c-kit+ CSCs involves the ischemic, inflammatory event itself that alters the heart’s microenvironment in a way that could make it inhospitable to CSCs. Hamid et al²⁰ found that traumatic ischemic events, such as myocardial infarctions, irreversibly alter the microenvironment of the heart via proinflammatory signals, such as TNF-alpha and other cytokines. This altered environment could lead to adverse cardiac remodeling and a lack of responsiveness and efficacy from c-kit+ CSCs.²⁰

Similarly, Mancuso et al,¹ stated that when macrophages enter the heart during an ischemic event, exogenous CSCs that were intended to be used for regenerative purposes were instead taken up by macrophages and degraded. First, bringing back the techniques applied by Alshammery et al¹⁷ and Sekiya et al,¹⁸ neither study explored varying numbers and arrangements of cells to achieve a different outcome than what their studies observed. Given the change noticed in those studies, perhaps Hamid et al²⁰ and Mancuso et al¹ would have ultimately collected different data as well. Additionally, Mancuso et al¹ mentioned the potential application of bioactive protein hydrogels that could help stabilize miRNA that is contained in the exosomes used to deliver CSCs exogenously, which would help in preventing their uptake and degradation by macrophages following an ischemic event.

Further, the last major argument against the use of this treatment resides in the fact that the details of this treatment are not yet understood. A study conducted by Hong et al²¹ found that although there were low levels of

differentiation into appropriate cardiac tissue following c-kit+ CSC treatment for an ischemic event, the treatment dramatically improved left ventricular systolic function through an unknown mechanism. The assertion that the use of c-kit+ CSCs should be avoided because they are not fully understood necessitates deeper exploration and may well find its answer as more research is conducted and becomes available in the future. However, it is worth noting that there were no major adverse effects reported in the study despite documentation of poor engraftment and adherence of the transplanted CSCs to the heart.²¹ This warrants further research and exploration into the area before it can be definitively stated that the risks of this treatment outweigh the benefits.

Conclusions

Current literature has well-established the specific benefits of c-kit+ CSCs compared with other stem cell types in treating ISD with stem cell transplantation, and other forms of regenerative cell therapy has offered valuable insights for future experimentation in the treatment of cardiac pathologies.

Various lineages of CSCs have been investigated for their potential in repairing the cardiovascular system, including Wt1-expressing Sca-1 and epicardial progenitor cells, which primarily offer protection for the vasculature. However, c-kit+ CSCs have garnered significant attention due to their ability to maintain the myocardium. While Sca-1 cells pose a lower risk of neoplasm formation, c-kit+ cells appear more suitable for use in ischemic heart disease due to their capacity to differentiate into smooth muscle, endothelial cells, and myocytes.¹ More recent clinical studies have also indicated the specific benefits of autologous c-kit+ myeloid cell populations in maintaining the viability of c-kit+ CSC transplants, another reason to further investigate how CSCs interact with other cell lineages in therapeutic stem cell transplants.²

CSCs were used in the CAREMI and SCIPIO trials in which patients had myocardial infarction and ischemic cardiomyopathy, respectively. Testing showed that with the treatment of CSCs, infarct size decreased (CAREMI) and LVEF increased (SCIPIO) over time. Within the 2 different approaches to these experiments, Bolli et al¹⁶ and Fernández-Avilés et al¹⁴ have developed arguments for the use of a less-invasive coronary artery infusion as opposed to surgery. Additionally, analysis of the CAREMI trial by Sanz-Ruiz et al provided insight into the use of autologous vs allogeneic CSCs, with the latter being the superior.¹³ This understanding is practical because in a damaged myocardium, CSCs may be dysfunctional due to the pathologic state of the heart. It is also worth noting that despite the positive results in the CAREMI trial, the power of the study was rather small, which can be an indication for a future randomized clinical trial of the same nature.

Finally, even within the population of c-kit⁺ cells themselves, only certain phenotypes have the ability to regenerate myocardium, arterioles, and capillaries. Specifically, Kubo, et al²² found that c-kit⁺ cells must commit to the cardiomyocyte lineage via the SMAD2 pathway to have myocardiocyte regeneration capability because c-kit⁺ cells committed instead to the blood/endothelial cell differentiation pathway did not beget regenerated myocardium.

Although more research is necessary to fully comprehend the effectiveness and safety of CSC therapy, the increasing amount of evidence indicates that allogeneic CSCs provide a secure and efficient approach to restoring damaged cardiac tissue and enhancing cardiac function. This review has highlighted various paths to achieve this objective, including gaining insight into how CSCs operate alone or in combination with other stem cells, understanding the function of CSCs in maintaining stem cell graft viability, elucidating the specific phenotypes of c-kit⁺ CSCs that carry myocardiocyte regeneration capability, safeguarding CSC function in a damaged heart, and comprehending why alternative therapies fail. Continued scientific inquiry into these avenues is critical for advancing the development of CSC therapy.

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