Stem Cell Therapy for Coronary Artery Disease

Assessing currently available data and selecting specific protocols for continued study of this therapy.

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Myocardial infarction (MI) remains one of the most common causes of mortality in the United States, accounting for one in three deaths. It is estimated that, on average, more than 2,200 Americans die from cardiovascular disease each day.[1] Treatment goals for acute MI aim toward rapid reperfusion times of the infarct-related artery, thus lowering the risk of permanent myocardial damage.[2] Therapeutic options include interventional, surgical, and pharmacological treatments in an effort to salvage ischemic myocardium. Despite faster reperfusion times, MI can still cause permanent and irreversible damage at the cellular level.[3] The restoration of these dead myocardial cells has led to the introduction of stem cell (SC) therapy in cardiovascular medicine. Recent advancements in SC therapy may hold the key to myocardial regeneration and improved cardiac mortality rates.

SC therapies for acute MI in animal models have shown promising results, yet human trials have yielded disparate outcomes.[4] A constellation of variables exist between presently available clinical trials of SC therapy—differing trial designs, SC sources, modes of SC delivery, and SC outcome measurements—creating inconsistencies in the interpretation of outcomes.[5]

CLINICAL DATA

Direct injection of SC therapy can be accomplished by various methods, but for the purposes of MI treatment, intracoronary (IC) delivery during percutaneous coronary intervention (PCI) seems to be the most feasible. Strauer et al was the first to report an IC delivery of bone marrow (BM)-derived SCs in a nonrandomized study of 10 patients 7 days post-PCI. They found a decrease in infarct size and perfusion defect, although no change in left ventricular ejection fraction (LVEF) was seen when compared to the control group at 3 months.[6] The TOPCARE-AMI trial was the first randomized trial using IC delivery of peripheral blood (PB)-isolated SCs to 30 patients and BM-derived SCs to 29 patients 5 days post-PCI. Both groups showed an improvement in LVEF at 4 months and a decrease in infarct size at 12 months; however, there was no control group in the trial for comparison.[7]

The BOOST trial, in contrast, studied 60 patients and used BM-derived SCs 5 days post-PCI in half of the patients, with the other half used as a control group. An improvement in LVEF was seen at 6 months by cardiac magnetic resonance imaging (MRI) in comparison to the control group.[8] The TACT-PB-AMI trial studied 54 patients in a nonrandomized fashion with IC delivery of PB-derived SCs 18 days post-PCI, which showed no improvement in LVEF at 6 months by ventriculography.[9]

Four of the largest randomized clinical trials performed using BM-derived SCs yielded conflicting results. The ASTAMI trial studied 100 patients, with half receiving SC therapy 6 days post-PCI, and demonstrated no significant change in LVEF by echocardiography, single-photon emission computed tomography (SPECT), or MRI at 6 months.[10] In contrast, the REPAIR-AMI trial recruited 204 patients, 101 of which received IC BM-derived SCs 4 days post-PCI, and revealed a significant improvement in LVEF as measured by quantitative ventriculography at 4 months.[11] The TIME trial enrolled 120 patients with reduced LVEF post-PCI for acute MI, randomized to receive BM-derived SCs at day 3 or day 7 postintervention and found a significant effect on global or regional LVEF compared with placebo at 6 months.[12] The SWISS-AMI trial randomized 200 patients with large acute MI to be treated with BM-derived SCs either early (5–7 days) or late (3–4 weeks) post-PCI and noted no significant improvement in LVEF at 4 months.[13]

TABLE 1. CLINICAL TRIALS OF STEM CELL THERAPY IN ACUTE MIA[a]

Study	Trial Design	Groups	Cell Type	Timing	Follow-Up	Primary Endpoint	Change in EF vs Control
Strauer[6] 2002	NR, C	PCI only (n = 10), BM SC (n = 10)	BM	PCI < 12 h post-MI, SC 7 d post-PCI	3 mo	LVEF by LVG	No change
Assmus[7] TOPCARE-AMI 2002	R, NC	PB SC (n = 30), BM SC (n = 29)	PB BM	PCI < 24 h post-MI, SC 5 d post-PCI	4 mo	LVEF by LVG	No control
Woolert[8] BOOST 2004	RC	PCI only (n = 30), BM SC (n = 30)	BM	PCI < 9 h post-MI, SC 5 d post-PCI	6 mo	LVEF by MRI	Increased by 6%
Tatsumi[9] TACT-PB-AMI 2007	NR, C	PCI only (n = 36), PB SC (n = 18)	PB	PCI < 6 h post-MI, SC 3 d post-PCI	6 mo	LVEF by LVG	Increased by 6%
Lunde[10] ASTAMI 2006	RC	PCI only (n = 50), BM SC (n = 50)	BM	PCI < 4 h post-MI, SC 6 d post-PCI	6 mo	LVEF by SPECT, echo, MRI	No change
Schachinger[11] REPAIR-AMI 2006	RC	PCI only (n = 103), BM SC (n = 101)	BM	PCI < 7 h post-MI, SC 4 d post-PCI	4 mo	LVEF by LVG	Increased by 3%
Traverse[12] TIME 2012	RC	PCI only early (n = 24), BM SC early (n = 43), PCI only late (n = 17), BM SC late (n = 36)	BM	PCI < 4 h post-MI, SC early 3 d post-PCI, SC late 7 d post-PCI	6 mo	LVEF by MRI	No change
Surder[13] SWISS-AMI 2013	RC	PCI only (n = 67), BM SC early (n = 65), BM SC late (n = 63)	BM	PCI < 5 h post-MI, SC early 6 d post-PCI, SC late 24 d post-PCI	4 mo	LVEF by MRI	No change
Valgimigli[15] 2005	RC	PCI only (n = 10), G-CSF (n = 10)	G-CSF	PCI < 12 h post-MI, G-CSF< 24 h post-PCI	6 mo	LVEF by SPECT	No change
Ince[16] FIRSTLINE-AMI 2005	RC	PCI only (n = 25), G-CSF (n = 25)	G-CSF	PCI < 5 h post-MI, G-CSF 90 min post-PCI	4 mo	LVEF by echo	Increased by 10%
Zohlnhofer[17] REVIVAL-2 2006	RC	PCI only (n = 58), G-CSF (n = 56)	G-CSF	PCI < 12 h post-MI, G-CSF 5 d post-PCI	5 mo	LVEF by MRI, LVG	No change
Ripa[18] STEMMI 2006	RC	PCI only (n = 39), G-CSF (n = 39)	G-CSF	PCI 4 h post-MI, G-CSF 28 h post-PCI	6 mo	LVEF by echo, MRI	No change
Takano[19] 2007	RC	PCI only (n = 22), G-CSF (n = 18)	G-CSF	PCI < 6 h post-MI, G-CSF < 24 h post-PCI	6 mo	LVEF by SPECT	Increased by 2%
Kang[20] MAGIC 2004	RC	PCI only (n = 10), G-CSF (n = 10), G-CSF+PB SC (n = 10)	G-CSF+PB SC	PCI < 48 h post-MI, G-CSF < 24 h post-PCI	6 mo	LVEF by SPECT	No change
Kang[21] MAGIC 3-DES 2006	RC	PCI only (n = 25), G-CSF+PB SC (n = 25)	G-CSF+PB SC	PCI 4 d post-MI, G-CSF < 24 h post-PCI	6 mo	LVEF by MRI	Increased by 5%

[a]*Adapted from Translational Research, Vol. 155, George JC, Stem cell therapy in acute myocardial infarction: a review of clinical trials, Copyright 2010, with permission from Elsevier.*[4]

Abbreviations: BM, bone marrow; C, controlled; G-CSF, granulocyte colony-stimulating factor; LVG, left ventriculography; NC, non-controlled; NR, nonrandomized; PB, peripheral blood; R, randomized; SC, stem cell; SPECT, single-photon emission computed tomography.

Indirect cytokine-induced mobilization of BM-derived SCs has also been shown to repair damaged myocardium and induce angiogenesis in animal models.[14] Granulocyte colony-stimulating factor (G-CSF) is a known stimulator of SCs and mobilizes BM-derived SCs into the peripheral circulation, resulting in improved myocardial function after MI. Valgimigli et al reported the first clinical trial using G-CSF in 20 patients with MI within 12 hours of PCI. After 4 days of treatment, there was no difference seen in LVEF by SPECT.[15] The randomized FIRSTLINE-AMI trial studied 50 patients, half of which received G-CSF 90 minutes post-PCI after MI for a period of 6 days. A significant improvement in LVEF was seen as early as 35 days.[16]

The REVIVAL 2 study looked at 114 patients and randomized 56 patients to receive G-CSF 5 days post-PCI for 5 days, which showed no benefit at 5-month follow-up.[17] Another trial with negative outcomes was the STEMMI trial, which recruited 78 patients and randomized 39 patients to receive G-CSF 28 hours post-PCI for 6 days; there was no significant difference in LVEF at 6 months.[18] Takano et al studied 40 patients with MI and enrolled 18 patients to receive G-CSF therapy within 24 hours of PCI for 4 days, demonstrating a significant improvement in LVEF by SPECT at 6 months.[19]

The combination of direct injection and indirect mobilization has also been studied. The MAGIC Cell trial recruited 27 patients with MI 24 hours post-PCI and treated 10 patients with G-CSF therapy alone for 4 days, 10 patients with G-CSF therapy for 4 days followed by IC injection of BM-derived SCs, and seven patients acted as a control group.[20] Although the G-CSF plus IC group demonstrated a significant improvement in LVEF at 6 months by SPECT in comparison to G-CSF group alone, there was no difference when compared to the control group. The MAGIC Cell-3-DES trial randomized 25 of 50 patients with acute MI to receive G-CSF post-PCI followed by an IC injection of BM-derived SCs.[21] After 6-month follow-up, there was significant improvement in LVEF by cardiac MRI in comparison to controls.

DISCUSSION

Demonstrating the existence of SCs and their capability to induce myogenesis or angiogenesis has led to the development of cell therapies that may be used for post-MI improvement of ventricular function as illustrated in both animal[22] and human studies.[4] However, the human clinical trials (Table 1) have been fraught with multiple variables across the studies, generating difficulty in interpreting the true outcomes of SC therapy.[5]

Study Design

Of all the SC trials that have been completed to date, the study design has varied between nonrandomized, randomized, and cohort studies without control groups. In a study by Cao et al, patients in the control arm experienced approximately 8% improvement in LVEF over baseline at 4-year follow-up.[23] The TOPCARE-AMI trial also demonstrated an 8% improvement in LVEF over baseline but without a control group.[7]

Sources of SCs

The lineage of SCs marks its capability to differentiate into various cell types. In the setting of MI, a majority of the trials have used BM-derived SCs due to feasibility. However, the TOPCARE-AMI[7] and TACT-PB-AMI[9] studies specifically evaluated PB-derived SCs. The TOPCARE-AMI trial demonstrated that the BM aspirate yielded > 665 times the cell product than from PB. The TACT-PB-AMI trial showed PB-derived SC to be comparable to BM-derived SC at improving post-MI LV function but required a time-consuming apheresis procedure to obtain adequate numbers of SC for therapy. The CADUCEUS trial utilized cardiosphere-derived SCs obtained from endomyocardial biopsies to treat 25 patients 2 to 4 weeks post-MI.[24] The authors reported significant improvement in scar mass, viable heart mass, regional contractility, and regional systolic wall thickening at 6 months, but a larger phase 2 placebo-controlled clinical trial is essential to validate these findings. Additional sources of SCs including allogeneic mesenchymal cells have demonstrated favorable results in ischemic cardiomyopathy and await further evaluation.[25]

Modes of SC Delivery

Direct injection of SC therapy can be accomplished through IC, intramyocardial, endomyocardial, retrograde coronary venous, and transvenous intramyocardial routes.[26,27] Although the best route is not known, IC delivery is the most feasible in the setting of MI and PCI. More recently, percutaneous transendocardial SC delivery has been demonstrated to be more accurate while maintaining safety and feasibility using bare fluoroscopy[28] or complementary electromechanical mapping.[29] Cell retention has been shown to be five to 15 times greater with transendocardial injections compared to intracoronary injections.[30]

Timing of Therapy

The timing of SC delivery varies dramatically among the currently available studies. The BALANCE study[31]

authors suggest that at 1 to 5 days post-MI, the inflammatory response is too strong for SC engraftment, but after 14 days, the initiation of fibrosis and scarring results in unlikely engraftment as well. The LateTIME trial investigators confirmed that SC therapy administered 2 to 3 weeks after acute MI did not improve global or regional LVEF at 6 months.[32] Therefore, the optimal timing of SC delivery is believed to be 5 to 14 days after the initial presentation of MI.

Outcome Measurements

LVEF has been the primary outcome measured in most of the clinical trials of SC therapy. However, the modality of LVEF measurement has been inconsistent with the use of left ventriculography, echocardiography, SPECT, and MRI.[5] The ASTAMI trial[10] utilized echocardiography, SPECT, and MRI and found no significant change in LVEF at 6 months. The REPAIR-AMI trial revealed that patients with the largest infarctions at baseline (post-MI LVEF < 48.9%) experienced the greatest benefit from SC therapy.[11]

SUMMARY

Several clinical trials using SC therapy for MI have been completed, and many more are well underway, including the largest trial to date—the BAMI trial[33] with targeted enrollment of 3,000 patients. The clinical trials conducted thus far have proven the safety and feasibility of SC therapy; however, the variability in study design, source of SC, mode of delivery, timing of therapy, and outcome measurements has resulted in ambiguity in interpretation of inconsistent results. Future trials of SC therapy will need to follow standardized protocols to determine the optimal utility of SC therapy for coronary artery disease. ■

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