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What is the future of cell-based therapy for Acute Myocardial Infarction

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Introduction

Although therapy for cardiovascular disease has led to consistent annual declines in mortality, myocardial infarction (MI) still represents an irreversible injury to the myocardium leading to the substrate for heart failure and sudden cardiac death[1]. Indeed, the extent of scar resulting from MI is an important predictor of mortality[2]. Even with timely coronary intervention, infarct size is a significant problem likely exacerbated by ischemia/reperfusion injury[3]. Supported by preclinical studies, cell-based therapy has emerged as an attractive treatment for minimizing/reversing the effects of MI in patients[4, 5].

Stem cell therapy following acute myocardial infarction (AMI)

Stem cell (SC) mobilization from the bone marrow to acutely injured tissue significantly enhancing wound healing was first observed in a mouse skin-wound model[6]. Large animal models demonstrated that SC therapy produces significant improvements in AMI[7,8], leading to clinical trials for SC therapy in patients with AMI and heart failure. Bone marrow-derived SC therapy for AMI is safe. Unfortunately, the hypoxic post-AMI environment is hostile to cardiomyocytes and migrating or introduced SCs, and this proapoptotic milieu may be the limiting factor clinically. However, a recent meta-analysis reported that patients with ischemic cardiomyopathy who received bone marrow-derived SCs exhibited improved left ventricular ejection fraction (LVEF), and reduced infarct size and remodeling[9] (Table).

CD34+ cells in clinical settings

Endothelial progenitor cells (EPCs) are bone marrow-derived mononuclear cells expressing both hematopoietic SC and endothelial cell markers. The prototypical EPC, selected on the basis of CD34 expression (CD34+), promotes neovascularization and regeneration[10]. The neovascular effects were demonstrated in a Phase I/II trial, where CD34+ EPCs administered to patients with refractory angina pectoris, decreased the frequency of events and increased

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exercise tolerance as compared to placebo-treated patients[11]. Furthermore, CD34+ EPCs mobilize from the bone-marrow post-AMI and enter the peripheral circulation; this degree of mobilization is directly correlated with improved outcomes[12]. However, large ischemic insults and adverse remodeling remain an extensive burden, even for efficient mobilizers. The extensive preclinical data supporting ischemic tissue repair by CD34+ cells prompted Quyyumi *et al.* to hypothesize that the effects of CD34+ cells were dependent on quantity and mobility following an ST Elevation MI (STEMI)[13]. They reported a positive dose-dependent improvement in cell mobility, cardiac perfusion, and scar size reduction following intracoronary infusion of CD34+ EPCs in subjects post-STEMI[13]. Those encouraging results inspired the current Phase II clinical trial (PreSERVE-AMI) to further elucidate the safety and bioactivity of autologous CD34+ marrow cells in patients post-STEMI[12].

PreSERVE-AMI Trial

The PreSERVE-AMI trial: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Intracoronary Administration of Autologous CD34+ Cells in Patients with Left Ventricular Dysfunction Post-STEMI, was novel and appropriately powered[12]. Subjects with successful stenting status-post-STEMI were randomized to receive autologous CD34+ cells (n=78) or placebo (n=81) via intracoronary infusion following bone marrow harvest.

The primary safety endpoints were adverse events (AEs), serious AEs (SAEs) and major adverse cardiac event (MACE). There were no differences between placebo and treated subjects in these categories. No differences were observed in survival or incidence of MACE in the treated group, regardless of dose ($p \geq 0.05$). AE and SAE incidence was similar between control and treated subjects at 12-month follow-up. The primary efficacy endpoint was improvement in resting myocardial perfusion over 6 months, which was not met, as there were no differences between groups. Furthermore, no changes in LVEF or scar size at 6 months were observed between groups. Despite primary endpoints not being met, post-hoc analyses were significant for reductions in infarct size, and changes in LVEF, after adjusting for total ischemia time. Additional testing with a larger patient population with allogeneic CD34+ cells may clarify the positive effects noted on tertiary analyses.

Impact of negative trials in regenerative medicine

While positive trials are enticing and provide a direction for the field of regenerative medicine, negative studies can be just as impactful. Negative studies move the field forward by avoiding repetition of ineffectual trials. Negative and positive trials save the field time and money, which in the end promotes higher quality study designs and conclusions.

Although the PreSERVE-AMI trial primary endpoint was not met, this failure does not negate the potential of CD34+ SCs to be an effective candidate for heart regeneration. Indeed, there are other instances in which SC trials face similar dilemmas in illustrating cell efficacy. Understanding these issues are key to interpreting the results of this study.

Factors to consider for interpretation of the PreSERVE-AMI trial results

1. Cell dose and cell source

In the study, post-hoc analysis favors a dose dependent response for improved LVEF and decreased scar. While general pharmacokinetics display a dose escalation response to a drug, such a response is not consistent for cell therapy. In fact, there are clinical trials that display higher response to lower cell doses[14], possibly due to the detrimental effects of cells (pathogenic angiogenesis, obstruction). These studies illustrate that the ideal dose for SCs has yet to be elucidated.

The patient population demonstrated a wide range of harvested cells, ($<20 \times 10^6$ to $>60 \times 10^6$). Furthermore, autologous SCs may be encumbered with baseline comorbidities (diabetes, age-related deficiencies), and thereby are likely possess lower potency as compared to allogeneic cells. The important advantage of allogeneic cells is highlighted by the fact that 16 (8%) patients from this study did not meet release criteria after bone marrow aspiration. Allogeneic cells can be produced in a quality controlled and cost-effective manner, and represent an off-the shelf option[7].

2. Timing of treatment

The time of cell infusion following stent placement was variable in this study, with a mean of 9.4 ± 1.43 and 9.3 ± 1.23 days for controls and treated patients, respectively. A meta-analysis of clinical trials utilizing adult bone marrow for the treatment of MI showed contradictory results in LVEF improvement secondary to timing of treatment, where later administration of cells proved more efficacious compared to early administration (<48 hours)[9]. Suppression of migration and proliferation in the SC niche is seen at times of excess inflammation (AMI). Cell therapy in the acute phase focuses on their anti-inflammatory and myocardial salvage traits; whereas, chronic treatment focuses primarily on regeneration capacities and reduction of adverse remodeling. The ideal timing post-transplantation for maximizing these effects has yet to be determined.

3. Route of administration

The optimal route of cell administration remains an area of uncertainty. Several methods are under investigation: trans-catheter endocardial, open-epicardial, intracoronary, intravenous and retrograde intra-coronary sinus. Despite these methods, the effects of SC treatment in AMI are limited. Without extracellular support (engineered tissue), evidence suggests that intramyocardial injection attains the highest number of retained cells despite their relatively low engraftment rate after an AMI[15]. As performed in this study, intracoronary injection is the preferred after an AMI because it avoids direct contact with the irritable myocardium thereby minimizing the risk of arrhythmia or perforation. The inherent disadvantage of intracoronary delivery is possible further occlusion of previously occluded arteries.

4. Trial size

Although the study was properly designed to power the primary efficacy endpoint, it is difficult to detect between group differences with limited sample sizes of Phase II trials. Furthermore, exploratory subgroup analyses, in this case, a dose dependent response of

CD34+ cells, are likely underpowered and hypothesis generating. Utilizing LVEF as an endpoint may have also obscured between group differences. In the AMI setting, LVEF can be misleading, as the hypokinetic wall motion is a result of a heterogeneous mix of infarcted and stunned myocardium. The cell treated group had a longer total ischemic time which implies they had larger infarcts and potentially a harsher environment further depriving the tissue of potential endogenous or exogenous cell repair. These complex confounding factors cannot be simply corrected by multiple regression models. Scar size as measured by MRI is a better endpoint, since as mentioned above, the extent of the scar is an important predictor of mortality[2].

Nonetheless, the number of larger Phase II and Phase III cell-based therapy trials for the treatment of heart disease trials is increasing, from 0 in 2014 and 2 in 2015, to 4 (including PreSERVE-AMI) in 2016. The Phase II CONCERT-HF (NCT02501811), Phase III DREAM HF-1 (NCT02032004) and BAMI (NCT01569178) trials are multicenter randomized trials currently enrolling an estimated 144, 600 and 3,000 patients, respectively.

Conclusion

Despite the failure to meet its endpoints, the PreSERVE-AMI trial ultimately represents an important step in the field of cardiac regeneration, by elucidating issues faced in the design of AMI trials. The hostile myocardial environment following AMI is a difficult hurdle to overcome for all progenitor cell types. This particular trial may have been affected by a number of unforeseen variables, including the use of autologous cells, which while immunotolerant, exhibit a decline in function with age and associated comorbidities (Online Figure). Autologous cell harvesting is also confounded by variable dosing, which may yield inconsistent results. Furthermore, the delay associated with the patients getting to the hospital for stenting means that time is an inherent ever-changing variable in an acute setting.

Despite the aforementioned variables, it is important to note that the use of CD34+ cells provide improvements in subjects when coronary oxygen demand exceeds its supply[11]. More importantly they proved to be safe in the current trial when compared to placebo. The safety of CD34+ cells will likely inspire further studies utilizing EPCs. The PreSERVE-AMI trial provides important insights regarding dosing of autologous CD34+ cells, time-to-treatment in an AMI setting, and safety. Moreover, the positive post-hoc analyses from this trial will undoubtedly lead to important new hypotheses to be tested in future trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conflict of Interest Disclosures:

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Table

Randomized Control Trials evaluating CD34+ bone marrow-derived stem cell therapy for Acute Myocardial Infarction

Source	Sample size	Cell type	Number of cells	Route of injection	Results
AMI					
Tendera *et al.* 2009	200	CD34+	NA	IC	No significant improvement
Quyyumi *et al.* 2011	31	CD34+	$5–15\times10^6$	IC	Dose dependent perfusion improvement
Quyyumi *et al.* 2016	161	CD34+	$8–43\times10^6$	IC	No significant improvement
ICM					
Patel *et al.* 2005	20	CD34+	NR	IM	Improved EF
Refractory Angina					
Losordo *et al.* 2007	24	Peripheral CD34+ + G-CSF	NR	IM	No significant improvement
Losordo *et al.* 2011	167	Peripheral CD34+ + G-CSF	$1–5\times10^5$/ Kg	IM	Improved angina and exercise tolerance in low dose group
Henry *et al.* 2016	112	Peripheral CD34+ + G-CSF	1–100 $\times10^5$/Kg	IM	Early termination of study Reduced angina frequency
NIDCM					
Vrtovec *et al.* 2013	110	Peripheral CD34+ + G-CSF	$1.13\pm0.26\times10^8$	IC	Improved EF, 6MWD Decreased NT-pro-BNP Lower mortality for stem cell treatment
Vrtovec *et al.* 2016	45	Peripheral CD34+ + G-CSF	$1.27–2.16\times10^8$	IM	No response in diabetics Increased EF, decreased NT-pro-BNP in non-diabetics

Abbreviations: AMI, acute myocardial infarction; EF, ejection fraction; G-CSF, granulocyte-colony stimulating factor; IC, intracoronary; ICM, ischemic cardiomyopathy; IM, intramuscular; NA, not available; NIDCM, non-ischemic dilated cardiomyopathy; NR, not reported; RCT, randomized controlled trial