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PERSPECTIVES

Moving Beyond Surrogate Endpoints in Cell Therapy Trials for Heart Disease

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SUMMARY

Cell therapy for heart disease began clinically more than a decade ago. Since then, numerous trials have been performed, but the studies have been underpowered, focusing primarily on low-risk patients with a recent myocardial infarction. Many data have accumulated on surrogate endpoints such as ejection fraction, but few clinical conclusions can be drawn from such studies. We argue here that the time is right for targeting larger and/or higher-risk populations for whom there is some expectation of being able to influence mortality or rehospitalization. STEM CELLS TRANSLATIONAL MEDICINE *2014;3:2–6*

INTRODUCTION

Heart disease is, and is predicted to remain, the single leading cause of death globally [1]. The fact that patients develop severe impairment of pump function indicates that the ability of the human heart to regenerate itself following injury is inadequate, despite persistence of endogenous cardiomyogenesis into adulthood [2]. Cell therapy, with the goal of regrowing lost healthy myocardium, is evolving as a potential therapeutic strategy for patients suffering from heart disease [3, 4]. An effective cell therapy would offer patients a regenerative option in addition to the currently available approaches, most of which are preventive or are aimed at attenuating disease progression.

During more than a decade of clinical trials of cardiac cell therapy, multiple cell types have been used in early phase (phase I and II) trials, primarily in the setting of acute or convalescent myocardial infarction (MI) [3, 4]. Bone marrow (BM)-derived cells have an established, excellent safety profile, but efficacy has been inconsistent and, overall, subtle [5–8]; however, unexpectedly meaningful benefits for clinical endpoints have been reported [9]. Early clinical experience with autologous heart-derived cells has been more encouraging in terms of surrogate endpoints. In the CADUCEUS trial [10], intracoronary infusion of autologous cardiosphere-derived cells (CDCs) [11] in post-MI patients with left ventricular (LV) dysfunction decreased scar size, increased viable myocardium, and improved regional function—findings that are consistent with myocardial regeneration. An interim analysis of the still-ongoing SCIPIO trial (using c-kit+ heart-derived cells) showed a remarkable increase in global LV function [12].

SURROGATE ENDPOINTS, CLINICAL EVENTS, AND PATIENT POPULATIONS

Although phase I and II trials offer important safety information and potential insights into bioactivity, the final and most crucial step in the pathway to clinical translation for cardiac cell therapy involves larger phase III trials (with the goal of establishing the efficacy of the new therapy over the current standard of care) [3]. Although regulatory agencies encourage, and academicians relish, the investigation of various exploratory endpoints in earlier phase trials, the primary endpoint of phase III trials should reflect clinically relevant effects (i.e., mortality, hospitalization, major adverse cardiac events) [13]. Endpoints such as ejection fraction and infarct size are not validated surrogates for clinical outcome and are not accepted by major regulatory agencies, such as the U.S. Food and Drug Administration, as primary efficacy endpoints for pivotal trials of novel therapies [13]. Nevertheless, surrogate endpoints figure prominently in the "go or no go" decision of whether to progress from small, exploratory studies to larger, appropriately powered trials designed to establish efficacy.

The majority of cell therapy trials to date have been performed in the setting of acute or convalescent MI and have enrolled patients who are not very sick (first-infarct population with minimal ventricular dysfunction [ejection fraction of ~50%] receiving aggressive, prompt reperfusion and optimal drug- and device-based therapies), leaving little room for improvement [3, 4]. This patient population has low mortality and morbidity, even without adjunctive cell therapy. For example, in the control group of the REPAIR-AMI trial (a well-conducted phase II multicenter trial of intracoronary delivery of BM mononuclear cells in patients with acute MI), 8 of 103 patients (7.8%) died and 5 of 103 patients (4.9%) were hospitalized for heart failure within 2 years of follow-up [9]. Thus, in the setting of acute or subacute MI, well-powered large-scale phase III trials with long-term follow-up would be required to show benefits in clinically meaningful endpoints. To that end, the Effect of Intracoronary Reinfusion of Bone Marrow-Derived Mononuclear Cells on All-Cause Mortality in Acute Myocardial Infarction (BAMI) study (ClinicalTrials.gov identifier NCT01569178) [14] will be conducted in Europe, with death as the primary endpoint; 3,000 patients with acute MI and ejection

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Table 1. Clinical trials of cell therapy in patients with chronic cardiomyopathy and heart failure

Cell type	Trial	Phase	Diagnosis	Delivery [dose]	New York Heart Association class	Effect on EF
Skeletal myoblasts	MAGIC [21]	II	ICM	IM (CABG) [400M, 800M]	80% II–III	No effect
	SEISMIC [43]	II	ICM	IM (catheter) [150-800M]	2.3 (mean)	No effect
Bone marrow-derived cells	Patel et al. [22]		ICM	IM (CABG) [22M CD34+]	3.5 (mean)	↑ ~10%
	Ang et al. [33]	II	ICM	IM/IC (CABG) [84M/115M MNCs]	16% III–IV	No effect
	Hendrikx et al. [32]		ICM	IM (CABG) [60M MNCs]	n.a.	No effect
	Stamm et al. [24]	I/II	ICM	IM (CABG) [5.8M CD133+]	2.6 (mean)	↑ ~6%
	TOPCARE-CHD [26]	I/II	ICM	IC [205M MNCs]	2.2 (mean)	↑ ~4%
	CELLWAVE [34]	I/II	ICM	IC (no shock) [90M MNCs]	2.3 (mean)	No effect
	TAC-HFT (pilot phase) [28]	I/II	ICM	IM (catheter) [100M, 200M MNCs/MSCs]	1.5 (mean)	No effect
	POSEIDON [29]	I/II	ICM	IM (catheter) [20M, 100M, 200M MSCs]	2.1 (mean)	No effect
	FOCUS-HF [30]	I	ICM	IM (catheter) [30M MNCs]	2.4 (mean)	No effect
	FOCUS-CCTRN [36]	II	ICM	IM (catheter) [100M MNCs]	2.3 (mean)	↑ ~3%
	MESOBLAST trial [31]	II	ICM plus non-ischemic dilated cardiomyopathy	IM (catheter) [25M, 75M, 150M STRO-3+ MSCs]	II–IV	No effect
	C-CURE [25]	II/III	ICM	IM (catheter) [605–1,168M cardiopoietic MSCs]	II–III	↑ ~7%
	TOPCARE-DCM [27]	I/II	DCM	IC [259M MNCs]	2.1 (mean)	↑ ~3%
Peripheral mononuclear cells	Erbs et al. [23]		ICM	IC [22–200M MNCs]	n.a.	↑ ~7%
	MAGIC Cell-3-DES (old myocardial infarction cohort) [35]	II	ICM	IC [140M MNCs]	n.a.	No effect
	TOPCARE-CHD [26]	I/II	ICM	IC [22M MNCs]	2.2 (mean)	No effect
Heart-derived cells	SCIPIO [12, 44]	I	ICM	IC [0.5–1M c-kit+ cells]	2.1 (mean)	↑ ~8% (4 mo)
	ALCADIA [37]	I	ICM	IM (CABG) plus basic fibroblast growth factor-loaded hydrogel [37M cardiac-derived cells]	3.8 (mean)	↑ ~12%

The difference in the treatment effect on EF between treated patients and controls (where available) is presented.
Abbreviations: CABG, coronary artery bypass grafting; EF, ejection fraction; IC, intracoronary; ICM, ischemic cardiomyopathy; IM, intramyocardial; M, million; MNCs, mononuclear cells; MSCs, mesenchymal stromal cells; n.a., not available.

fraction (EF) <45% will be randomized to either conventional therapy or intracoronary infusion of autologous BM mononuclear cells. The BAMI study is powered to detect a 25% relative decrease in 2-year all-cause mortality after cell therapy (11.5% vs. 8.6%). Although this highly anticipated study will hopefully answer, once and for all, whether BM mononuclear cells are a useful adjunctive therapy in acute MI, the low event rates with standard care undermine the potential public health importance of the findings.

Heart Failure: High Event Rates Offer a Key Opportunity to Evaluate Efficacy of Cell Therapy

In contrast to acute and convalescent MI, heart failure represents a more fertile target for outcome trials, given the much higher event rates. In the EVEREST trial of vasopressin antagonism (New York Heart Association class, 3–4; mean EF, 27%), 26% of patients receiving optimal medical treatment died and 46% died or were hospitalized for cardiovascular causes during a median follow-up of 9.9 months [15]. The respective percentages in the ACCLAIM trial of immunomodulatory therapy (New York Heart Association class, 2–4; mean EF, 23%) were 10% (death) and 36% (death or cardiac rehospitalization) during a mean follow-up of 10.2 months [16]. Apart from the higher event rates, targeting a heart failure patient population offers an additional advantage: multiple lines of evidence from the first decade of cell therapy clinical trials suggest that sicker patients are the ones who benefit the most from administered cells [5, 7, 8, 17]. Thus, cell therapy could maximize its potential by targeting an advanced heart failure population comprising critically ill patients who stand to benefit dramatically, not incrementally, from experimental treatments.

What has been the experience to date with cell therapy in heart failure? Several cell types have been tested in clinical trials with symptomatic heart failure patients; these are summarized in this paper (Table 1). Early small trials delivering skeletal myoblasts via intramyocardial injectons to patients with chronic ischemic cardiomyopathy and heart failure showed a functional benefit, albeit with a high incidence of arrhythmia [18–20] (a problem that

does not seem to be associated with delivery of BM- and heart-derived cells). Preliminary results from the first placebo-controlled skeletal myoblast trial (MAGIC) showed a trend toward improved remodeling at 6 months [21]; however, this trial was discontinued prematurely for lack of efficacy apparent in an interim analysis.

Other studies examined the safety and efficacy of BM-derived cells, administered by intracoronary infusion or intramyocardial injections (open chest or catheter guided) in patients with chronic (predominantly ischemic but also nonischemic) cardiomyopathy and heart failure. The results of those studies have been inconsistent, and functional benefits have ranged from strongly positive (Patel et al. [22], Erbs et al. [23], Stamm et al. [24], C-CURE [25]) to marginally positive (TOPCARE-CHD [26], TOPCARE-DCM [27], TAC-HFT [pilot phase] [28], POSEIDON [29]), mixed (FOCUS-HF [30], Mesoblast [31]), and negative (Hendrikx et al. [32], Ang et al. [33], CELLWAVE [no shock plus cell therapy arm] [34], MAGIC Cell-3-DES [old MI cohort] [35], FOCUS-CCTRN [36]). In one study (POSEIDON [29]), a head-to-head comparison of allogeneic (donor derived) and autologous (self-derived) BM mesenchymal stromal cells (MSCs) was performed in patients with chronic ischemic cardiomyopathy and heart failure. The major finding of POSEIDON was that therapy with allogeneic MSCs appears to be safe and at least as active as therapy with autologous MSCs. Another study, performed exclusively with allogeneic STRO-3+ MSCs, did not reveal any significant immune reaction to the administered cells [31]. Taken together, early, small pilot clinical studies of BM-derived cells in patients with chronic cardiomyopathy and heart failure have shown hints of modest efficacy; however, the results of these underpowered, preliminary, and—for the most part—suboptimally designed studies (nonrandomized, open label, or noncontrolled) have been inconsistent, and primary endpoints understandably focused on safety rather than efficacy.

Recent results from clinical application of heart-derived cells in patients with chronic ischemic cardiomyopathy and heart failure have been more promising, but the published experience remains small. An interim analysis of the still-ongoing SCIPIO trial revealed that intracoronary infusion of c-kit+ cells (in surgically revascularized patients with ischemic cardiomyopathy) improved global and regional function, heart failure symptoms, and quality of life [12]. The findings of decreased scar size and increased viable myocardium in treated patients are encouraging but must be tempered by the lack of data in any control subjects. An interim analysis of the still-ongoing ALCADIA trial revealed that intramyocardial injection of heart-derived cells in patients undergoing surgical revascularization improved global and regional function [37] (ALCADIA uses heart-derived cells similar to CDCs in combination with a basic fibroblast growth factor-loaded hydrogel [38]).

Our sense is that heart failure is a most attractive target for cell therapy. The field needs to move beyond small exploratory studies focused on surrogate endpoints of questionable predictive value to larger trials appropriately designed to assess hard, outcomes-based endpoints.

Considerations for the Design of Future Clinical Trials

Moving forward, beyond surrogate endpoints and toward trials powered to test clinical efficacy, familiar questions arise: which patient population, which method of delivery, and what cell type should be tested? As noted previously, heart failure likely represents a more fertile target for outcomes trials because of significantly higher event rates and (potentially) greater efficacy of cell therapy in this sicker patient population. With regard to methods of cell administration, both the intracoronary and intramyocardial routes have been used for delivery of cells into failing hearts (Table 1). Intramyocardial delivery (either open chest or catheter based) results in better cardiac cell retention [39], can access unperfused myocardial regions, and can allow for delivery of high numbers of cells (up to 1 billion cells [25]) that would be microembolic if delivered intracoronarily; however, it is invasive and results in highly localized cell distribution (around the injection sites) [40]. In contrast, intracoronary delivery may result in suboptimal cardiac cell retention, and delivery of larger cells requires appropriate dosing and optimization of the infusate [41]; however, it is simple in execution and enables homogenous distribution of cells across large myocardial regions [40]. Intracoronary infusion into multiple coronary vessels, allowing for delivery of higher total cell doses (compared with infusion into one artery only) and greater myocardial coverage, seems particularly intriguing [42] for heart failure patients. We have found that intracoronary delivery of CDCs is just as efficacious as catheter-mediated intramyocardial delivery, despite the increased cardiac cell retention (and the much greater technical difficulty) of the latter (unpublished observations). Finally, with regard to the choice of cell type, BM-derived cells have been proven to be safe and (possibly) modestly efficacious. The very limited clinical experience with heart-derived cells suggests that such cells may have a higher regenerative capacity, but it remains to be shown whether they offer increased clinical benefits.

These considerations lead us to favor a high-risk heart failure population for future trials. With regard to the choice of cell type and delivery method, our personal preference tilts toward heart-derived cells delivered via multiple coronary arteries to achieve widespread distribution within the myocardium; however, there is considerable uncertainty regarding cell type and delivery method. Comparative studies would be most welcome, so as to maximize the likelihood of eventual success.

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Author Contributions

K.M.: collection and/or assembly of data, data analysis and interpretation, manuscript writing; E.M.: conception and design, financial support, data analysis and interpretation, manuscript writing, final approval of manuscript.

Disclosure of Potential Conflicts of Interest

E.M. and K.M. have uncompensated consultant/advisory roles with Capricor, Inc., and E.M. has a compensated ownership interest in Capricor, Inc.

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