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Is There a Role for Intravenous Stem Cell Delivery in Non-Ischemic Cardiomyopathy?

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The delivery of stem cells to the heart in the setting of ischemic or non-ischemic cardiomyopathy has almost exclusively relied on intramyocardial (IM) or intracoronary (IC) routes of administration. This strategy is based on several preclinical (1) and human studies (2) demonstrating minimal engraftment of cells in the heart when delivered by an intravenous (IV) infusion and the demonstration that higher engraftment in the heart is associated with greater improvement in LV function (3,4). In patients with non-ischemic cardiomyopathy, Vrtovec et al. (2) randomized 110 patients to IC autologous $CD34^+$ stem cells (n=55) or control. Over a 5-year period, those patients randomized to IC delivery of $CD34^+$ cells had a higher event-free survival and sustained improvements in left-ventricular ejection fraction (LVEF) and exercise capacity by 6-minute walk test (6MWT). In a subgroup of patients (N=43) that received labeled cells to measure engraftment (5.7% at 18 hours), only those patients with homing above the median sustained an improvement in LVEF at 1-year supporting the importance of cell engraftment in mediating efficacy. In a second study (4), the same group compared IC versus IM delivery of the same dose of $CD34^+$ stem cells to a similar group (n=40) of patients with non-ischemic cardiomyopathy. They observed that retention of cells measured by SPECT at 18 hours following delivery was 4-fold greater by IM delivery versus IC (19.2 vs. 4.4%) and that IM delivery was associated with a significantly greater increase in LVEF (8.1 vs. 4.2%) and 6MWT distance at 6 months. These findings strongly support the concept that the initial engraftment of cells strongly correlates with improved LV function and exercise capacity.

Fate of Intravenous Delivered Stem Cells

Imaging of IV delivered radiolabeled stem cells in humans and animals reveal that the vast majority of cells initially traffic to the liver and spleen. Larger cells such as MSCs are initially trapped in the lung but redistribute to the liver and spleen 24 hours later (5). Only a small signal is detected in the myocardium following IV delivery suggesting that there is

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minimal cardiac uptake. However, any uptake that occurs appears preferential to the infarct zone confirming that stem cells may home to areas of myocardial injury (6). In a small study of 17 patients with acute or chronic infarction, IC delivery of ^{18}F-FDG labeled peripheral hematopoietic stem cells resulted in a 1.5% uptake in the infarct zone by PET imaging 2 hours after injection that persisted for 20 hours (2). The vast majority of cells were retained in the liver and spleen. In a subgroup of 3 patients who underwent IV stem cell infusion, the majority of cells were trapped in the lungs with no activity detected in the heart 4 hours later. Hofmann et al. (7) compared IV vs. IC delivery of 18F-FDG labeled bone marrow mononuclear cells in patients following ST-elevation myocardial infarction (STEMI). No significant retention in the myocardium was detected in the heart by PET imaging following IV cell delivery compared to 1.3 to 2.6% radioactivity retention following IC delivery that was greatly enhanced when selected CD34+ cells were injected. However, because this study only imaged the acute (1-hour) uptake in the heart, it is possible that redistribution of cells to the heart could occur at later time points.

Indeed, this redistribution was demonstrated by Kraitchman et al. (5) who delivered ^{111}In oxine-labeled allogeneic canine MSCs by IV delivery following myocardial infarction. They demonstrated an increasing signal in the infarct region 24 hours after infusion by SPECT/CT imaging as the cells were redistributed to the heart and other organs following initial lung entrapment. This increased signal observed with MSCs following IV delivery compared to other progenitor cells may suggest that they have higher homing capabilities. Alternatively, because of their larger size, they are more easily trapped in the coronary microcirculation. For that reason, IC delivery of MSCs has generally been avoided (1)

Given that engraftment is so poor with IV delivery, why would it be undertaken in a clinical study? In 2005, OSIRIS Therapeutics Inc. initiated the first randomized, placebo-controlled Phase 1 clinical trial of allogeneic MSCs (0.5, 1.6, 5.0 × 10^6 cells/kg) delivered by IV infusion following acute myocardial infarction in 53 patients (8). They observed that IV MSCs were safe and improved global assessment of well-being, pulmonary mechanics (FEV1) and suppressed arrhythmias compared to placebo. Overall, no change in LV function was noted between groups, but the subset of patients with anterior MIs had a statistically significant improvement in LVEF compared to placebo. Based on these encouraging findings, a second trial was initiated and completed several years ago. Unfortunately, the manufacturer has not released the data to the Investigators.

A Clinical Trial of IV Cell Delivery in Non-Ischemic Cardiomyopathy

In this issue of *Circulation Research*, Butler, Epstein and colleagues (9) administered allogeneic ischemia-tolerant MSCs (itMSCs) (1.5 × 10^6 cells / kg) by IV in fusion in 22 patients with non-ischemic cardiomyopathy. This is the first cardiovascular cell therapy trial to utilize MSCs cultured under hypoxic condition, thus mimicking the hypoxic microenvironment in the bone marrow. MSCs secrete a broad range of cytokines with anti-inflammatory and immunomodulatory activity and this novel strategy can theoretically produce a cell product with greater paracrine activity and homing ability (10) that may increase engraftment.

In a 90-day crossover design, they observed that itMSCs had no effect on LV function or volumes, but significantly improved the patient's functional status as measured by 6-minute walk distance (+ 36.5 m) and the Kansas City Cardiomyopathy Questionnaire score (+5.2). They further observed that the itMSC infusion was associated with a significant increase in CD3 and CD4 T-cell levels and a decrease in the number of natural killer (NK) cells at 30 days. NK cells are cytotoxic lymphocytes critical to the immune system that the authors have previously found to mediate adverse LV function and remodeling in a murine myocardial infarction model that can be suppressed by itMSCs. In support of this, the authors observed that the reduction in NK cells following itMSCS infusion between baseline and 90 days correlated inversely with the improvement in LVEF in a *post-hoc* analysis. A subset of the T-cell population, regulatory T-cells (Treg) that are $CD4^+CD25^+Foxp3^+$, may suppress T-cell proliferation and cytokine production that may mitigate the persistent inflammation in CHF. However, levels of Tregs are reduced in heart failure and lower levels are an independent predictor of worsening heart failure and hospitalization (11). Unfortunately, the various subsets of CD4 T-cells including Tregs were not identified in this study so it remains unclear if the itMSCs increased levels of Tregs that could contribute to the improved functional status observed in this study.

Of interest, the itMSC effect on CD3/4 and NK cells waned at 90 days suggesting that the immunomodulatory effects of the itMSCs may be transient and would require repeat infusions to produce a durable effect. As a result, the 90-day follow-up of the patients in this study may be too short to determine the duration of the functional improvement observed in this study. Because this was the first cardiovascular cell therapy trial to administer preconditioned MSCs, one wishes that data had been provided to support the authors' contention that these cells are endowed with greater cytokine production than standard MSCs.

The disconnect between the lack of improvement in LV function and greater functional status in this trial deserves comment. This was not the case in the recently published POSEIDON-DCM Trial (12) of 34 patients with non-ischemic cardiomyopathy randomized to allogeneic versus autologous MSCs. In that study, a similar dose of 100 million MSCs was delivered to a sicker non-ischemic patient population by intramyocardial injections with NOGA (Biosense Webster, Diamond Bar, CA). In patients who received allogeneic MSCs (n=18), there was a significant improvement in LV function (+8% LVEF) and functional status as measured by 6MWT. The results of this study and others (3,4) suggest that the engraftment produced by an IV infusion is likely insufficient into improve both LV function and functional status.

So how can stem cells improve functional status without improving LV function? A growing consensus has emerged that heart failure is associated with a heightened inflammatory state that contributes to progressive decline in LV function and exercise intolerance. Increased production of reactive oxygen species leads to impaired nitric oxide bioavailability and endothelial dysfunction which may impair vasodilation of the microcirculation and peripheral arteries and contribute to exercise intolerance, a hallmark of this disorder. It is possible that the systemic delivery of itMSCs in this study improved endothelial function which enhances exercise capacity as measured by the 6MWT. In support of this, patients

with cardiomyopathy treated with allogeneic MSCs demonstrate improved endothelial function via forearm-mediated vasodilation and have increased endothelial progenitor cells colony forming units (EPC-CFU) (13).

Potential Benefits of Intravenous Delivered Allogeneic Stem Cell Therapy

Allogeneic stem cell infusion by an IV route of administration potentially offers several advantages over IC or IM delivery. An IV allogeneic off-the-shelf product could be administered at any health care facility at a delivery cost that is miniscule compared to an IC or IM route that requires delivery in a cardiac catheterization laboratory. Allogeneic cells harvested from a young healthy donor may be superior to an autologous product obtained from older patients with coronary artery disease or other co-morbidities (14). IM delivery frequently requires electromechanical mapping and injections with the NOGA system or helical injection catheter (Biocardia Inc., San Carlos, CA) that is limited to a few experienced sites. Currently, there are only 62 NOGA sites in North America. Additionally, although intramyocardial injections are relatively safe, there remains a 1– 2% risk of perforation and tamponade.

As suggested in this study, the duration of benefit of cell therapy may be limited as evidenced by the loss of statistical significance over time of the measured T-cell and NK cell populations. This is likely to be a common problem in all types of cardiovascular cell therapy regardless of route of administration as the retention of cells in the myocardium quickly wanes. Thus, a recent pre-clinical study convincingly demonstrated in a 30-day old rat infarct model that repeat injections of stem cells over time were superior to a single injection in mediating the recovery of LV function and reduction of scar size (15). Repeat injections would likely be cost- and safety-prohibitive using an IC or IM route of administration making IV therapy a necessity if the duration of benefit is limited.

Going Forward

The prospects of using an allogeneic MSC product delivered by an IV infusion has many attractive attributes. The improvement in functional status of patients in this clinical trial is encouraging but future studies are needed to more fully assess the potential benefits of IV delivery and the robustness of itMSCs. Going forward, there should be head-to-head comparisons of single dose versus repeated dosing that incorporate adequate follow-up time to assess the durability of benefit. Additionally, studies should evaluate whether ischemia-tolerant MSCs produce a greater functional benefit than standard allogeneic MSCs. Although allogeneic MSCs are advertised as being immunoprivileged, this has never been tested in a clinical trial of repeat dosing.

In contrast to ischemic cardiomyopathy, the origins of non-ischemic cardiomyopathies are diverse. Early trial results suggest that a non-ischemic etiology may portend a better response to cell therapy in heart failure patients. It is likely that the clinical response will vary with the etiology, yet these are rarely identified in clinical trials. Patients with a history of myocarditis may respond differently to cell therapy than a patient with a genetic

cardiomyopathy. Future studies will need to do a better job of stratifying the different types of non-ischemic cardiomyopathies in assessing their response to cell therapy.

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