MRI Tracking of the Regional Persistence of Feridex-labeled Mesenchymal Stem Cells in a Canine Myocardial Infarction Model

A. V. Soto[1], W. D. Gilson[1], D. Kedziorek[1,2], A. Tal[1], D. Crawford[1], P. Karmarker[1], R. G. Young[3], M. F. Pittenger[4], J. W. Bulte[2], D. L. Kraitchman[1]

[1]Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University, Baltimore, MD, United States, [2]Institute for Cell Engineering, Johns Hopkins University, Baltimore, MD, United States, [3]Osiris Therapeutics, Inc, Baltimore, MD, United States, [4]Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD, United States

Introduction:

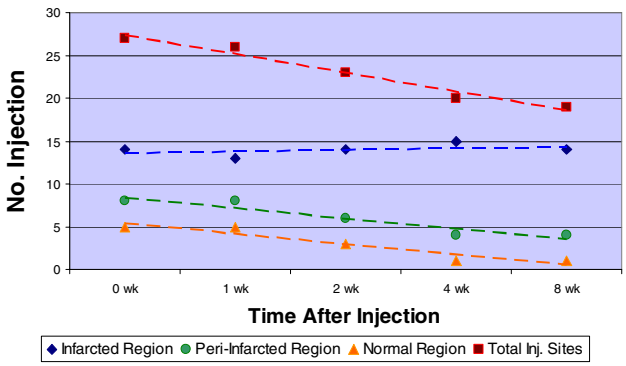
Due to the limited ability of the heart to regenerate after an ischemic event, cellular therapy has shown promise as a method to provide cytokines and cells to participate in the repair process. However, the understanding of whether the efficacy of cellular therapies is due to the transient or ongoing presence of exogenously delivered cells in current clinical trials is uncertain due to the inability to image the cellular therapeutics *in vivo*. Superparamagnetic iron oxide (SPIO) labeling of stem cells[1] combined with MR imaging offers a method to track the persistence of cellular therapeutics and target the delivery of these cells using a transmyocardial approach to specific regions of injury, such as the infarction border. The purpose of this study was to determine the regional persistence and migration of targeted SPIO-labeled mesenchymal stem cells (MR-MSCs) in a canine model of myocardial infarction over 2 months.

Methods:

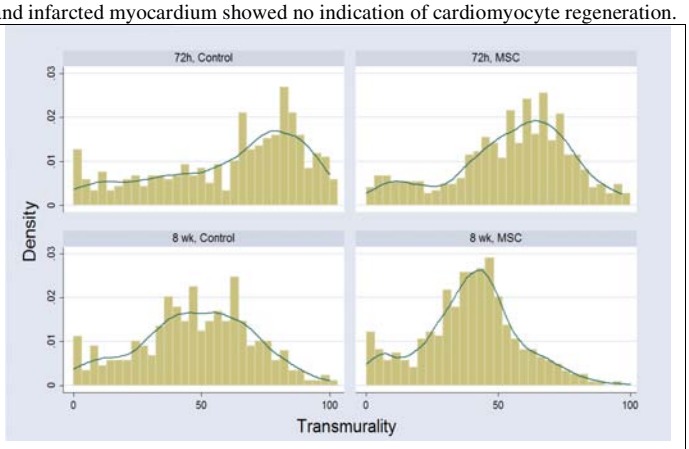
Seven dogs (25-30 kgs) were subjected to a 90-minute closed-chest coronary artery occlusion followed by reperfusion to create an acute myocardial infarction (AMI). Autologous MSCs were isolated and magnetically labeled with 25 µg Fe/ml Feridex and 375 ng/ml poly-L-lysine for 24 hours prior to delivery.[2] At 72 hours post-AMI (T=0 wk), delayed contrast-enhanced (DCE) MRI (1.5 T GE CV/*i*) was performed to determine the infarct location. Subsequently, each dog received 30-190x10^6 MR-MSCs (7x10^6 MSCs/injection) under MR fluoroscopy.[3] Contiguous fast gradient echo (FGRE) high resolution short-axis images (TR/TE=6/1.6 ms; 0.5x0.5x5mm voxel; 2 NSA; 20º FA; 32 kHz BW) were obtained to localize injection sites. Imaging was repeated at 1, 2, 4, and 8 weeks post-injection to assess persistence of MR-MSCs. A 6 sector/slice model was used to track regional persistence and migration of MR-MSCs. Each sector was classified according to infarct status, i.e., infarct (I), peri-infarct (PI), and normal (N), based on DCE images. The relationship of stem cell persistence was corresponded to infarct transmurality using a 36 sector/slice model and compared to historical non-MSC-treated AMI dogs (n=5).

Results:

At 72 hrs post-AMI, hypointensities corresponding to MR-MSCs were present in all three regions with 52% in I, 30% in PI, and 19% in N. The persistence of individual stem cell injection sites is shown in Figure 1. In particular, migration occurred into the I and PI regions such that 37.5% of original PI injections migrated to I and 20% of original N injections migrated to PI. Over the 2 month follow-up, original injection sites disappeared: 21% in the infarcted region, 25% in the adjacent region, and 60% in the normal region. The infarct (Figure 2) showed a significant shift to decreased transmurality from 0 to 2 months in the MSC-treated dogs versus the non-MSC-treated AMI dogs. Histological analysis of injection sites in adjacent and infarcted myocardium showed no indication of cardiomyocyte regeneration.



Graph 1: Number of stem cell injections is shown by imaging session and region as well as the composite total injection numbers. Injections decreased over time normal and peri-infarcted regions with the normal region showed the greatest diminution of injections sites.



Graph 2: Histogram of infarct transmurality data for the treated (right) and control (left) dogs at 0 (top) and 8 (bottom) weeks. A distinct shift in transmurality can be seen in the treated dogs that received MSCs in contrast to the control dogs.

Conclusions:

Traditional imaging techniques, such as DCE and high resolution imaging, can be used to accurately target and track stem cells. The higher tendency of the MSCs to remain in the infarcted and peri-infarction site throughout the eight week span indicates that these areas may be the preferred for targeting. The more than 25% reduction in injection sites over two months represents a combination of stem cell death and stem cell migration. Serial MR imaging of MR-labeled stem cells could provide a method for tailoring therapy to individual patients as well as for targeting therapy to the areas with the highest likelihood of efficacy.

References:

[1] Frank et al. *Radiology*, 2003; 228: 480-7
[2] Kraitchman DL et al. *Circulation,* 107(18):2290-2293, 2003
[3] Karmarkar et al., *Magn Reson Med,* 51(6):1163-72, 2004