Coronary Sinus Delivery of SDF-1 Plasmid for the Treatment of Heart Failure

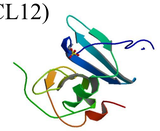
Juliana Woda, PhD[1], Scott J. Fisher, PhD[1], Joseph Pastore, PhD[1], Amit Patel, MD, MS[2], Rahul Aras, PhD[1], Marc Penn, MD, PhD[1,3]

[1]Juventas Therapeutics, Cleveland, Ohio; [2]University of Utah, Salt Lake City, UT [3]Summa Health, Akron OH

Background

- SDF-1 is an 8 kDa chemokine that promotes tissue repair through recruiting stem cells, promoting vasculogenesis and preventing apoptosis
- Preclinical and clinical studies (Phase I and II) have demonstrated transendocardial delivery of a SDF-1 expressing non-viral DNA plasmid (pSDF-1) is safe and may result in myocardial repair following ischemic injury
- Retrograde infusion through the coronary sinus provides an alternative route to transendocardial delivery

SDF-1 (CXCL12)



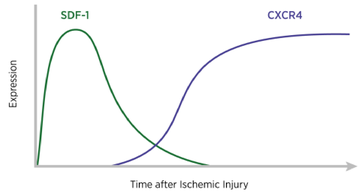


Figure 1. SDF-1 and CXCR4 expression after an ischemic injury
SDF-1 expression is temporarily increased after an injury but soon fades, whereas the primary SDF-1 receptor, CXCR4, is continually upregulated in ischemically damaged tissue.

Hypothesis:

Retrograde coronary sinus infusion of a non-viral gene therapy, pSDF-1, to the myocardium following ischemic injury is safe and efficacious

Expression Studies

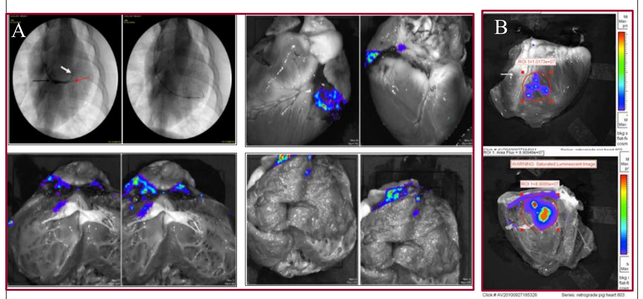


Figure 2. Feasibility of non-viral DNA plasmid Coronary Sinus Delivery
Using a luciferase reporter plasmid (pSDF-1 backbone) demonstrates that the gene can be delivered via coronary sinus occlusion and expresses protein into (A) non infarcted and (B) infarcted hearts. Luciferase expression shown 3 days post infusion assessed via Xenogen imaging

Methods

Induce myocardial infarction : 90 minute LAD balloon occlusion

4 weeks

Treatment:
- Placebo (5% Dextrose)
- pSDF-1 (15 mg) in 5% Dextrose
- pSDF-1 (45 mg) in 5% Dextrose

Delivered via retrograde coronary sinus infusion

+ 3 days → Safety, biodistribution

+ 60 days → Safety, biodistribution, efficacy

Procedure : Retrograde Coronary Sinus Infusion
- CS access (jugular vein access)
- Insert balloon catheter
- Inflate balloon to occlude CS, confirm occlusion with contrast agent
- Infuse 40 ml of pSDF-1 or vehicle over 2 minutes
- Maintain occlusion for 10 minutes
- Deflate balloon

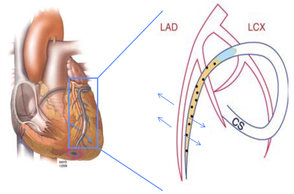


Figure 4: Retrograde Coronary Sinus Infusion
Retrograde coronary sinus infusion is performed by using a balloon catheter to occlude the coronary sinus. The therapeutic, pSDF-1, or vehicle is infused through the lumen. Occlusion is maintained for 10 minutes post delivery to ensure uptake.

Results

Safety

- Administration of the pSDF-1 via retrograde coronary sinus perfusion was not associated with any adverse effects including any mortality, clinical findings, changes in body weights, adverse electrocardiographic findings, changes in clinical pathology endpoints or adverse macroscopic or microscopic findings.

Biodistribution: Day 3

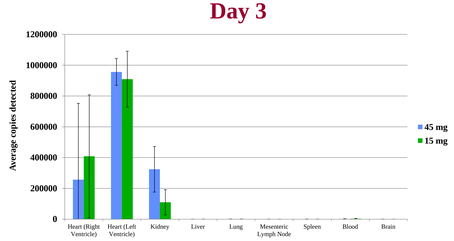


Figure 3. pSDF-1 biodistribution following retrograde delivery
Quantitative qPCR was used to examine the biodistribution of plasmid 3 and 60 days following retrograde delivery. The highest level number of copies were found in the heart. Plasmid was also detected in the kidney. Low levels of plasmid were detected other non target organs. Plasmid was cleared from all organs except the heart by day 60 (data not shown). This distribution pattern is the same as the pattern found following endomyocardial delivery

Results

Efficacy

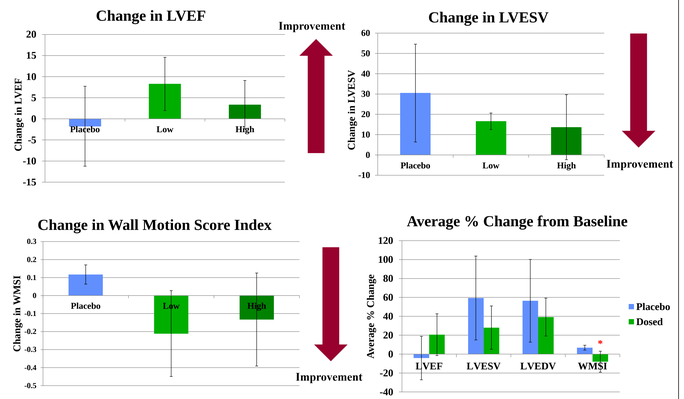


Figure 5. Delivery of pSDF-1 showed improvement in cardiac function and remodeling
Sixty days following pSDF-1 delivery, a trend in improvement from baseline in left ventricular ejection fraction (LVEF, 5.8 % ± 2.2) and left ventricular end systolic volume (LVESV, (15.1 ml ± 3.9 ml) compared to placebo (LVEF: -1.8 %± 4.7 , LVSESV: 30.5 ml ± 12 ml) was observed in treated animals. Significant improvement was observed in WMSI in treated animals ((-0.17± 0.08) compared to untreated animals (0.117 ± 0.03, $p \leq 0.032$).

RETRO-HF Trial

- Preclinical studies demonstrated that retrograde coronary sinus infusion (RCSI) of the plasmid results in myocardial protein expression and RCSI delivery of pSDF-1 was safe and effective in a porcine model of ischemic heart failure
- To test the safety and efficacy of pSDF-1 delivered by retrograde coronary sinus infusion in ischemic heart failure patients, the RETRO-HF was initiated.
- RETRO-HF is the first FDA allowed trial for retrograde coronary sinus delivery of a biologic
- **RETRO HF is a Phase I/II (12 subject) open label, dose escalation / (60 subject) randomized, placebo controlled, double-blind study** being conducted at 15 participating centers. All patients will have an EF ≤40%. All patients will be dosed on day 0 with 40 cc pSDF-1 via coronary sinus occlusion using the Oscor Venos CS Occlusion Catheter. Safety will be assessed at 3 days, 1, 4 and 12 months post-injection. Efficacy will be assessed at 4 and 12 months.

Trial Design:

- 12 subject, open-label, dose escalation, phase I
- 60 subject randomized, double-blind, placebo controlled phase II
- 6MWD* <400 m, MLWHFQ# score > 20, EF < 40%
- Randomization to 3 Cohorts (1:1:1): Placebo; 30 mg; 45 mg
- 12 month follow-up
- pSDF-1 delivered via CS infusion using the Oscor Venos Balloon

* 6MWD: 6 minute walk distance # MLWHFQ: Minnesota Living with Heart Failure Questionnaire

Endpoints

- **Structural (echo):** LVEF, LVESV, LVEDV, WMSI
- **Functional**: 6MWD, MLHFQ, NYHA Class
- **Clinical**: HF Decompensations, MACE, Hospitalizations
- **Biomarkers**: NtproBNP, Galectin-3

Major Inclusion/Exclusion

Major Inclusion Criteria:
- Symptomatic Ischemic Cardiomyopathy
  - MI at least 6 months ago
  - EF≤35%, 3 contiguous LV with abnormal WMSI
- 6 Minute Walk Distance (6MWD) ≤400 m
- Optimal Pharmacological Therapy
  - Beta blockers
  - Diuretics
  - ACE Inhibitors and/or ARB
  - Statin unless contraindicated

Major Exclusion Criteria:
- Active cancer other than non-melanoma skin cancer
- Scheduled for revascularization in next 30 days
- Scheduled for mitral valve repair or replacement
- BiV pacemaker (lead in CS) or previous CS trauma

Recruitment Dates

The study began enrolling in November 2013 and plans to end recruitment in August 2014 (NCT01961726)

Conclusions

- Retrograde coronary sinus infusion of plasmid into the heart results in protein expression in the myocardium within two to three days following delivery.
- pSDF-1 is primarily delivered to the heart following retrograde CS infusion with some distribution to the kidneys. Plasmid was cleared from all organs except the heart by day 60. The biodistribution pattern of plasmid following retrograde coronary sinus infusion is similar to the pattern seen following endomyocardial injection of the plasmid.
- Delivery of pSDF-1 via retrograde CS infusion in a porcine model of heart failure was safe and did not result in any adverse effects.
- In a porcine model of heart failure, delivery of pSDF-1 via retrograde CS infusion resulted in a trend towards improvement in cardiac function and remodeling as measured by LVEF, LVESV, LVEDV. Wall motion score index was significantly improved in treated animals compared to placebo.
- Based on these results, we initiated a 72 patient Clinical Phase I/ II trial to test safety and efficacy of delivery pSDF-1 plasmid via retrograde CS infusion to treat ischemic heart failure.