DREAM-HF

- **CONDITION:** Chronic Heart Failure
- **PI:** Mosi Bennett, MD
- **CONTACT INFO:** Jane Fox, RN | Jane.Fox@allina.com | 612-863-6289
- **DESCRIPTION:** The primary objective of this study is to determine whether the investigational transendocardial delivery of allogeneic human bone marrow-derived MPCs (rexlemestrocel-L) is effective for chronic heart failure due to LV systolic dysfunction.

- **CRITERIA LIST/QUALIFICATIONS:**
  - The patient has a diagnosis of chronic HF of ischemic or nonischemic etiology for at least 6 months.
  - The patient is on stable, optimally tolerated dosages of HF therapies including beta-blockers (approved for country-specific usage), angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), and/or aldosterone antagonists, without change in dose for at least 1 month before study intervention.
  - The patient is on a stable, outpatient, oral diuretic dosing regimen in which the patient remains clinically stable during screening.
  - NYHA class I & IV are excluded.
- **SPONSOR:** Mesoblast LTD
DREAM-HF

• Phase 3 double blind, placebo controlled, clinical trial
• One of the largest stem cell trials
• **Mesenchymal Precursor Cell (MPC)** strategy
  • Bone marrow derived cells from healthy donors
  • Expanded and stored until use
  • Proven efficacy in animal and clinical models of heart failure
• **Primary Objective**: determine if the trans-endocardial delivery of MPCs is effective for the treatment of chronic systolic heart failure
• MPCs are injected into viable myocardium using a mapping system
• **Primary Endpoint**: a composite of cardiac death or heart failure event
DREAM-HF Inclusion Criteria

We are looking for:

- Ischemic or non-ischemic cardiomyopathy patients
- EF < 40%
- On a stable heart failure and diuretic regimen
- NYHA class II or III symptoms
- At least 1 heart failure hospitalization in the last 9 months
- or ER visit requiring an IV diuretic
- or NT-proBNP > 1000 pg/ml
DREAM-HF

• As of September 2017:
  • 423 patients enrolled across 66 sites
  • 10 patients enrolled at MHIF (10th overall)
  • A recent interim analysis of efficacy and safety was successful

• PI: Mosi Bennett, MD PhD

• CONTACT INFO: Jane Fox, RN | Jane.Fox@allina.com | 612-863-6289
Mapping the future of CMR?

David Lin, MD
10/02/2017

♥ Conflict of interest: none
Case based format

What’s T1 mapping and extracellular volume (ECV)

T2 mapping and it’s clinical utility

CMR use in non-MR and MR conditional implantable devices

Case

69 yo male with longstanding history poorly controlled HTN and medication non-compliance, OSA, morbid obesity, and CAD (previous proximal LAD stent) admitted with community acquired pneumoniae and TnI 0.088
- Hypertensive cardiomyopathy
- Ischemic cardiomyopathy
- HCM
- Amyloid
- Other

LVEF 45%
LVH = 21mm
Hypertensive cardiomyopathy
Ischemic cardiomyopathy
HCM
Amyloid
Athletic heart
Anderson-Fabry’s
Other
What’s wrong with current sequences

- Traditionally, cardiologists rely on changes in LVEF and morphology to distinguish health and disease.
- With CMR, late gadolinium enhancement (LGE) became the non-invasive gold standard in detecting scar, which is fundamental in the development of myocardial dysfunction in various cardiomyopathies.
- However, LGE underestimates extent of interstitial fibrosis.
- In the setting of diffuse fibrosis, abnormality could go undetected by LGE due to absence of a normal reference standard within the myocardium.
- Contraindication to gadolinium (i.e., GFR <30)

What’s T1 mapping

- T1 describes how quickly proton recovers after being “flipped” by a radiofrequency pulse.
- It measures the fundamental property of tissue. T1 is determined mostly by H20 and fat content. Water prolongs T1 and fat shortens it.
Why T1 mapping

- T1 mapping can quantify global and regional perturbation in myocardial structure, without concurrent need for a reference “normal”
- Allows detection of focal and diffuse myocardial process without gadolinium. Essentially, assessing tissue composition
- T1 is changed in disease states
- Biomarker?
- Derive extracellular volume (ECV)

T1 mapping, evidence

- Increased native T1:
  - T1 increases with myocardial water content, protein deposition, fibrosis
  - DCM
  - Amyloid
  - HCM
  - MI
  - Myocarditis
Native T1 Mapping in Transthyretin Amyloidosis

Fontara et al.

Figure 3. Native T1 in Healthy Volunteers, Mutation Carriers, HCM, Definite AL, and Definite ATTR

Mean native myocardial T1 ± 2 SE in healthy control subjects, gene carriers, patients with definite AL cardiac amyloidosis, and patients with definite ATTR cardiac amyloidosis. Abbreviations as in Figure 2.

Native T1
= 1152
T1 mapping evidence

- Decrease T1:
  - Sensitive and specific in Anderson Fabry’s and cardiac siderosis.
    - Fabry’s: LVH similar to amyloid and HCM. Lipid accumulation likely -> decrease in T1 (distinguish Fabry’s from other forms of LVH).
    - Iron overload: iron shortens all CMR relaxation times (T1, T2, T2*). More sensitive than T2*. 
Beyond native T1 mapping, gadolinium can be used to determine extracellular volume (ECV). ECV is a quantitative measure of the volume % of interstitial space. Has high agreement with histologic measures of myocardial collagen content.

ECV particularly valuable in disease that produce diffuse interstitial remodeling and expansion (amyloid, post MI, HCM, AS … etc).

ECV strongly associates with mortality.
ECV = (1 – haematocrit) \left( \frac{1}{\text{post contrast } T_1 \text{ myo}} - \frac{1}{\text{native } T_1 \text{ myo}} \right) \left( \frac{1}{\text{post contrast } T_1 \text{ blood}} - \frac{1}{\text{native } T_1 \text{ blood}} \right)

requires gadolinium contrast

Native T1 = 1152

Post-contrast

ECV = 46%
Biopsy confirmed cardiac amyloidosis.
Mass spectrometry showed ATTR variant.
Genetic testing revealed val142lle mutation consistent with hereditary amyloidosis.
T1 = 1152 msec, ECV 46%, BNP 196. After recovery from pneumoniae, patient without functional limitations.
Case

- 72 yo admitted due to urinary retention after recent back surgery. Incidentally noted to be in atrial fibrillation.
- Cardiac PMH otherwise negative.
Discharged with rate control and out-patient cardiac MR scheduled.

2 days later, patient readmitted with SOB
Native T1 = 1165
ECV = 69%
BNP 410

Genetic testing was consistent with wild type amyloid (senile)
Plein et al, Cardiac T1 Mapping and Extracellular Volume in clinical practice: a comprehensive review, JCMR; 2016; 18:89

Magnetic Resonance in Transthyretin Cardiac Amyloidosis

[Graphs showing survival function for ECV in different conditions]
Treatment

**Amyloidogenic TTR Cascade**

- **Liver**
  - TTR Tetramer
  - TTR Monomer
  - Misfolded State
  - Amyloid Fibril

**Mechanism of Action**

- **Suppression of Amyloidogenic TTR**
- **TTR Stabilization**
- **Fibril Degradation**

**Silencers**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Potential Index</th>
<th>Phase (IV)</th>
<th>Route</th>
<th>Dose</th>
<th>Drug Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASO</td>
<td>Suppresed the TTR mRNA and protein levels.</td>
<td>Phase 2</td>
<td>IV/QD</td>
<td>300 mg</td>
<td>ISG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mTRA</td>
<td>Silences the TTR gene to reduce TTR production.</td>
<td>Phase 3</td>
<td>IV/QD</td>
<td>5 to 7 mg/kg</td>
<td>Ely Lilly</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Stabilizers**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Potential Index</th>
<th>Phase (IV)</th>
<th>Route</th>
<th>Dose</th>
<th>Drug Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tafamidis</td>
<td>Inhibits the degradation of amyloid fibrils.</td>
<td>Oral</td>
<td>2 mg/QD</td>
<td>Pfizer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diflunisal</td>
<td>Reduces the production of TTR.</td>
<td>Oral</td>
<td>210 mg/QD</td>
<td>Ely Lilly</td>
<td></td>
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</tr>
</tbody>
</table>

**Disruptors**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Potential Index</th>
<th>Phase (IV)</th>
<th>Route</th>
<th>Dose</th>
<th>Drug Company</th>
</tr>
</thead>
</table>
| Disruptors | TTR-
| Deposition | | | | | | |

**References**

Castano et al, Emerging Therapies for Transthyretin Cardiac Amyloidosis Could Herald a New Era for the Treatment of HFPEFm, Latest in Cardiology, ACC, Oct 14, 2015
♥ 57 yo with poorly controlled HTN (BP 171/108 at clinic), obesity (310 lbs), and OSA presents SOB.
- Hypertensive cardiomyopathy
- Ischemic cardiomyopathy
- HCM
- Amyloid
- Athletic heart
- Anderson-Fabry’s
- ? But no further work up needed
Native T1 = 1024
ECV = 26%
Hypertensive cardiomyopathy
Ischemic cardiomyopathy
HCM
Amyloid
Athletic heart
Anderson-Fabry’s

Native T1 mapping and ECV provide prognostic value beyond EF and LGE.
It’s also prognostic in dilated non-ischemic cardiomyopathy.
T1-Mapping and Outcome in Nonischemic Cardiomyopathy

ECV

Table 2. The ECV Was Associated With Outcomes in Multivariable Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mortality Outcome (n=39)</th>
<th>Death, Cardiac Transplant, or Left Ventricular Assist Device Outcome (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECV (for every 3% increase)</td>
<td>1.55 (1.27-1.88)</td>
<td>1.48 (1.23-1.78)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (for every 5% decrease)</td>
<td>1.23 (1.11-1.37)</td>
<td>1.29 (1.16-1.43)</td>
</tr>
<tr>
<td>Myocardial infarction size tertile</td>
<td>1.13 (0.81-1.57)</td>
<td>1.15 (0.86-1.55)</td>
</tr>
<tr>
<td>Age (for every 10- years increase)</td>
<td>1.29 (1.02-1.64)</td>
<td>1.17 (0.94-1.46)</td>
</tr>
</tbody>
</table>

The χ² statistic measures the strength of association between the predictor variable and the outcome. ECV indicates extracellular volume fraction.

(Circulation, 2012;126:1206-1216.)
Case

38 yo, previously healthy, admitted with 6 months hx of DOE and recent syncope. TnI 0.09
Native T1 = 1180
ECV 50%
Endomyocardial biopsy was positive for amyloidosis.
Mass spectrometry consistent with AL (kappa) amyloid.
Bone marrow biopsy plasma cell myeloma.
T1 mapping and survival in systemic light-chain amyloidosis

Banypersad et al, EHJ, 2015, 36, 244-251

100 confirmed AL amyloid patients

T1 mapping/ECV

- Non-invasive characterization of myocardium previously only possible with cardiac biopsy
- New biomarker
- Improve diagnosis in difficult and rare diseases
- Prognostic importance and refine risk stratification
T1 mapping/ECV

- Not hard to do but hard to do well
- Despite promising native T1 and ECV data, significant overlap in disease processes.
- Variation in normal T1 depending on CMR vendors and magnet (1.5 vs 3.0T).
- No clear standardization of normal values and protocols between vendors and institutions.

Case

- 15 yo with acute onset chest pressure.
- TnI > 20.
- TTE normal LVEF without wall motion abnl.
♥ Cath
♥ CTA
♥ CMR
♥ All of the above
♥ Clinical diagnosis, not further work up
T2 mapping

- Traditional T2W imaging
  - Stagnant blood pool contamination
  - Breath hold and rhythm dependent
  - Image interpretation is subjective
- T2 value increases with water content
- Similar to T1 mapping, pixel wise map is generated from T2 decay curve
- With any acute inflammation, T2 increases
- Allows quantitative assessment of myocardial disturbance
- Essential in cases where there’s no apparent injury by LGE or in patients where gadolinium is contraindicated.
T2-STIR

T2 mapping
T2 mapping

- Current CMR protocol in patients with myocarditis and tako-tsubo focuses on:
  - Wall motion abnormalities
  - Myocardial delayed enhancement
  - Subjective T2W STIR interpretation

- Problematic:
  - WMA may not be grossly apparent
  - LGE may be absent
  - T2W STIR technical limitations
Averaged T2 values in the involved and remote segments in patients with myocarditis (N=20) and tako-tsubo cardiomyopathy (TTCM) (N=10) and controls (N=30) are shown.


Receiver operating characteristic curves

Case

- 73 yo with hx of CVA, DM, OSA, and hyperlipidemia admitted with SOB.
- Acute onset, while working at the Vikings stadium.
- TnI 0.060
T2 mapping

♥ Identifies areas of acute injury even in the absence of LGE.
♥ Distinguishes acute from chronic event.
♥ Quantitative assessment vs subjective evaluation.
♥ Avoid typical T2W-STIR technical limitations.
CMR and implantable devices

Case

- 64 yo with ischemic CM due to previous anterior MI (s/p LAD stent).
- s/p ICD (non-MRI conditional) in 2015 due to persistent LV dysfunction.
- Admitted electively for left and right heart cath due to exertional chest discomfort, PND, and weight gain.
- TnI 0.022
> 2 million patients in the US have implanted devices, including pacemakers and ICDS.

It’s estimated > 50% will require MRI sometime after device implantation.

Concern that magnetic field and radiofrequency energy can cause device malfunction and permanent damage including tissue lead interface -> absolute contraindication.
Non-conditional devices

- In early 2000s, uncomplicated experience with MRI performed inadvertently on patients with devices lead to discussion about safety of MRI on this population.
  - MRI was performed safely in all patients
  - 16% cardiac
  - 3 patients developed power on reset
- All CMR requests are reviewed by EP and CMR reader. Devices assessed before and after CMR.

Device and artifacts

- LGE is the gold standard non-invasive evaluation of various forms of cardiomyopathy.
- Guides catheter ablation and assess viability.
- Devices (ICD and pacemakers), however, produces hyper-intense artifacts in LGE sequences, preventing diagnostic evaluation.
Device and artifacts

- High intensity artifacts are caused by off resonance produced by the generator. Spins in the affected myocardium are not inverted by the IR pulse.
- A wideband sequence replaces the standard bandwidth, eliminating the artifact.
Contraindication to CMR in patient with non-conditional devices:
- Epicardial leads
- Baseline device or lead malfunction
- Implant < 6 weeks
- Pacemaker dependent patients with ICD if asynchronous pacing mode not available
- Abandoned or cut endovascular leads

Case
- 57 yo Canadian male, otherwise healthy, was training for a marathon when noted sudden drop in exercise tolerance. Heart block was observed, MR compatible PPM placed.
- Developed acute onset palpitation and pre-syncope in his hotel room while visiting the Twin Cities.
- EMS called, found to be in VT with HR in the 250s, cardioverted x 1.
- TTE normal LV function. RVE and mild dysfunction.
Univariate Cox proportional hazard models for the total population demonstrating that the presence of LGE has a hazard ratio of 24.5 (5.3–112.9; P<0.01) for death or ventricular tachycardia (VT).


Kaplan–Meier curves demonstrating the impact of cardiac sarcoidosis on survival in the late gadolinium enhancement (LGE)+ (red) and LGE− (blue) groups

MR conditional devices

- Much less artifact, even with SSFP cine imaging
- Simplified programming to MR “safe” mode.
  - VOO for pacer dependent patients
  - OOO for non-pacing dependent patients
  - Increase pulse amplitude and duration to reduce risk of loss of capture
- Hardware changes:
  - Decrease ferromagnetic components
  - Coil design to minimize lead heating and induction
  - Replacement of reed switch
- Near zero complication rate

Summary

- T1 mapping and ECV are complementary tool to current CMR sequences.
- Tissue characterization by native T1 has the potential to be the source of diagnostic, therapeutic, and prognostic decision making especially in patients where gadolinium is contraindicated.
- Following T1 changes in myocardium overtime in patients with cardiomyopathies or receiving cardiotoxic drugs
Summary

- May serve as a new “non-invasive histologic marker”
- Refines risk stratification and improves diagnosis.
- Not yet for prime time as a stand alone sequence.
  - Overlap between different cardiomyopathies
  - Overlap with normal T1 values
  - Lack of true “normal” values across vendors
- Must be interpreted within clinical context, like all medical tests

Summary

- T2 mapping is a robust tool in assessing inflammatory cardiomyopathies
  - It is relative insensitive to cardiac and respiratory motion
  - Offers quantitative instead of subjective qualitative evaluation
- Cardiac MR is safe in non-conditional devices.
  - Protocols should be followed.
  - LGE evaluation diagnostic.