Update on Novel Therapeutic Approaches to Heart Failure

24th Annual Heart Failure 2020: Update on Diagnosis and Therapy
Los Angeles, California
March 14, 2020

Barry Greenberg M.D.
Distinguished Professor of Medicine
Director, Advanced Heart Failure Treatment Program
University of California, San Diego
Evolution of Heart Failure Therapy

- **1700’s - 1960’s**: Dig and diuretics
- **1970’s**: Vasodilators
- **1980’s - 2019**: Neurohormonal Antagonists
  - The Remodeling Paradigm
  - Myocardial Mechanics

*The Age of Empiricism*
Therapies That Improve Outcomes in Heart Failure Patients

**Drugs**
- ACEIs/ARBs/ARNIs
- Beta blockers
- Aldosterone receptor antagonists
- Hydralazine/nitrates (in AAs)
- Ivrabadine
- Diuretics…probably
- Dig…maybe

**Devices**
- BiV pacemakers
- ICDs
- LVAD’s
- PA pressure sensors

**Other**
- Cardiac Transplant
Recent Advances in Heart Failure Management

- **Prevention**
  - SGLT2 inhibitors for treating T2DM
  - New target goals for treating HTN

- **Treatment**
  - SGLT2 inhibitors for HFrEF
  - MRA's for HFpEF
  - Novel therapies for treating amyloidosis
  - Advances in MCS
Why Do We Need New Therapies For Heart Failure?

• Minimal progress in treating HFpEF and little change in outcomes after AHF hospitalization.

• Current HFrEF treatments are palliative, not curative.
Outcomes in HFP EF, HFr EF and HFmr EF

Shah KS et al, Journal of the American College of Cardiology, Volume 70, Pages 2476-2486

Delepaule et al. ESC HF. 2017 May; 4(2): 99–104
New and Emerging Strategies

**Drugs**
- Vericiguat
- Omecamtiv mecarbil

**Biologics**
- Gene transfer Rx
- Stem cell Rx

**Strategies**
- Machine learning to identify patients at high risk
sGC Regulates CV Function

Heart Failure
- oxidative stress
- inflammation
- endothelial cell dysfunction

sGC stimulators

Myocardial Function
Relaxation, Diastolic stiffening, Energy utilization

Vascular Function
Endothelium-dependent vasomotor tone

sGC, soluble guanylate cyclase; NO, nitric oxide; eNOS, endothelial NO synthase; cGMP, cyclic guanosine monophosphate
**SOCRATES: Vericiguat**

### Primary endpoint

- **Primary analysis:** NT-proBNP reduction in pooled 2.5/5/10 mg dose groups > reduction in placebo (NS, *p*=0.1506)

- **Secondary analyses:**
  - Dose-response relationship in primary endpoint NT-proBNP (*p*=0.0174, exploratory only)
  - NT-proBNP reduction in 10 mg group > placebo (*p*=0.0483; pre-specified pairwise comparison, exploratory only)
SOCRATES: Exploratory Endpoints

**Time to composite of HF hospitalization and CV death**

**Event-free survival (proportion of patients on treatment)**

**Treatment Group**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.97 (0.50-1.88)</td>
</tr>
<tr>
<td>1.25 mg</td>
<td>1.01 (0.52-1.94)</td>
</tr>
<tr>
<td>2.5 mg</td>
<td>0.63 (0.30-1.34)</td>
</tr>
<tr>
<td>2.5 to 5 mg</td>
<td>0.53 (0.25-1.16)</td>
</tr>
<tr>
<td>2.5 to 10 mg</td>
<td>0.72 (0.41-1.26)</td>
</tr>
</tbody>
</table>

**Observation period**

- **Until week 12**
  - CV death or HF hospitalization
    - Placebo (N=92): 18 (19.6%)
    - 1.25 mg (N=91): 17 (18.7%)
    - 2.5 mg (N=91): 18 (19.8%)
    - 2.5 to 5 mg (N=91): 11 (12.1%)
    - 2.5 to 10 mg (N=91): 10 (11.0%)

- **End of F/U**
  - Death (all-cause)
    - Placebo (N=92): 6 (6.5%)
    - 1.25 mg (N=91): 6 (6.6%)
    - 2.5 mg (N=91): 5 (5.5%)
    - 2.5 to 5 mg (N=91): 3 (3.3%)
    - 2.5 to 10 mg (N=91): 4 (4.4%)

Hazard Ratio (HR) and CI derived from Cox Proportional Hazard model. Hazard ratio and CIs are calculated, if minimum number of 5 events in total and 1 event in each treatment arm exist. Hospitalization and deaths are adjudicated by an independent adjudication committee and classified as CV or non-CV. Vericiguat/Placebo. FAS, full analysis set.
Design of Phase 3 VICTORIA Study

VICTORIA MET ITS PRIMARY ENDPOINT

Primary endpoint: Time to first event for HF hospitalization or CV death
Omecamtiv Mecarbil (OM) - A Selective Cardiac Myosin Activator

Mechanochemical Cycle of Myosin

OM increases the entry rate of myosin into the tightly-bound, force-producing state with actin

“More hands pulling on the rope”

- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in dP/dt_{max}
- No increase in MVO₂

Efficacy of Omecamtiv Mecarbil in COSMIC

A  Systolic ejection time (msec) at Week 20

B  Stroke volume (mL) at Week 20

C  Left ventricular end-systolic dimension (mm) at Week 20

D  Left ventricular end-diastolic dimension (mm) at Week 20

Efficacy of Omecamtiv Mecarbil in COSMIC

NT-proBNP, N-terminal of the prohormone brain natriuretic peptide

GALACTIC-HF

Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility (in Heart Failure)

An 8,000 Patient Event Driven Double-blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects With Chronic Heart Failure With Reduced Ejection Fraction
Gene Transfer Therapy for Treating Heart Failure

- Introduction of recombinant human genetic material to a patient in order to alter levels of a protein that will directly or indirectly (e.g. paracrine or systemic effects) alter cardiac structure and function.
Danon Disease (DD)

- Rare genetic disorder estimated to affect ~ 15,000-30,000 people in the US and EU – males generally more severely affected

- Caused by a mutation in the *LAMP2B* gene (*Lysosomal Associated Membrane Protein 2B*) that leads to severe impairment in autophagic flux

- Mainly presents with HCM phenotype, but in females, may be DCM

- May also present with muscle weakness and cognitive impairment

- Diagnosis confirmed by genetic testing

- Generally cannot be managed medically or with device intervention – rapid progression in males and requires LVAD (mechanical pump) or heart transplant

- Gene transfer therapy using an AAV9 vector has been used to successfully treat animal models of Danon Disease
Caused by loss of function mutation in LAMP2b gene that results in impaired autophagy within cardiomyocytes and other cells throughout the body.
Survival in Patients with Danon Disease

Recombinant AAV9 Vector Expressing *LAMP2B*

- **RP-A501**: Assigned name for Rocket product, AAV9.LAMP2B
- **AAV9**: Adeno Associated Virus serotype 9
- **CAG**: (C) the cytomegalovirus (CMV) early enhancer element, (A) the promoter, the first exon and the first intron of chicken beta-actin gene, (G) the splice acceptor of the rabbit beta-globin gene
- **CBA**: Chicken β actin promoter
- **RbG**: RNA binding Glycine Rich
- **WPRE**: Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element
- **RGpA**: Arginine-specific cysteine protease
- **ITR**: Inverted terminal repeat sequence
Clinicaltrials.gov: https://www.clinicaltrials.gov/ct2/show/NCT03882437?cond=Danon+Disease&rank=2

Contact:
Barry H Greenberg, MD 858-657-5267
bgreenberg@ucsd.edu

Phirum Nguyen, 858-822-3108
psnguyen@ucsd.edu

Or contact Rocket Pharmaceuticals, Inc at:
danonclinicaltrial@rocketpharma.com
Mesenchymal Precursor Cells (MPCs)

- Highly purified population of bone marrow-derived mesenchymal stem cells isolated using STRO-3 Ab.

- Negative for HLA Class II antigens, do not express CD80 and CD86 co-immunostimulatory molecules have immunomodulatory effects in vitro.

- Can be expanded and formulated as a cryopreserved “off the shelf” product.

- Given to allogeneic recipients via iv, sc, im, ic routes without donor matching or immune-suppression.

- Likely MOA involves stimulation of endogenous cardiac repair via cytokine/growth factor secretion.
NOGA-XP Mapping System

MyoStar Delivery Catheter

Revascor Phase 2 Heart Failure Study:
Delivery of MPCs to the Myocardium
MPCs Improved Outcomes in Patients With Ischemic CM

Time-to-First HF-MACE by Treatment
(36 Months Follow-up)

150M MPC vs Control
P-value = 0.025
based on log-rank test

DREAM-HF

Multicenter, double-blind, RCT, scripted sham procedure, controlled parallel group trial using a single dose of 150 million MPC’s injected into 20 LV sites.

Enrolled patients with symptomatic HFrEF (EF<0.40) receiving optimal GDMT

Includes patients with either ischemic or non-ischemic etiology

Primary endpoint is a composite of cardiac death or HF hospitalization
Predicting mortality in heart failure (HF) is critically important to patients, their providers, healthcare systems, and third-party payers alike.

Accurate prediction of risk, however, has proven to be a difficult task.

Machine learning (ML), which has long been used by other fields (e.g. high-energy physics) to discriminate between signal and background, uses non-parametric analysis methods to incorporate these interactions.

We extracted data from the HER at UCSD and applied ML techniques to generate a risk score to predict mortality in HF patients.
Machine Learning to Predict Outcomes

Predictive regardless of LVEF, gender, in-patient or out-patient setting

Adler E, Greenberg B et al. Eur J HF 2019
MARKER-HF Predicted Outcomes in Other Patient Populations

Supplementary Table 4. Performance of MARKER-HF, GWTG-HF Risk Score and the ADHERE Risk Score in the UCSD, UCSF and BIOSTAT-CHF Populations.

<table>
<thead>
<tr>
<th>Population</th>
<th>AUC for MARKER-HF</th>
<th>AUC for GWTG-HF</th>
<th>AUC for ADHERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSD</td>
<td>0.875 ± 0.027</td>
<td>0.736±0.015</td>
<td>0.626±0.014</td>
</tr>
<tr>
<td>UCSF</td>
<td>0.810 ± 0.045</td>
<td>0.758±0.037</td>
<td>0.644±0.026</td>
</tr>
<tr>
<td>BIOSTAT-CHF</td>
<td>0.835 ± 0.060</td>
<td>---*</td>
<td>0.599±0.045</td>
</tr>
</tbody>
</table>

*Absence of collection of key variables in the BIOSTAT-CHF data base required for calculating risk using the GWTG prohibited generation of an AUC in this population. For the same reason, we were unable to evaluate IMRS scores on UCSF and BIOSTAT-CHF cohorts.

Adler E, Greenberg B et al. Eur J HF 2019
Evolution of Heart Failure Therapy

- Dig and Diuretics
  - The Age of Empiricism
    - 1700’s - 1960’s

- Vasodilators
  - Myocardial Mechanics
    - 1970’s

- Neurohormonal Antagonists
  - The Remodeling Paradigm
    - 1980’s - 2019

- Gene Transfer
  - Cell Therapy
  - Use of AI
    - 2020 -

- Artificial Intelligence and Molecular Revolution
Thank You!