The Future for HF Therapy

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Stem Cell/Gene Therapy for CV Dis.

DISCLOSURES

Company | Role            | Study
---------|-----------------|------
Juventas  | Nat/Site PI     | STOP-PAD
Mesoblast | Site PI        | DREAM
Athersys  | Site PI        | NSTEMI
Leonhardt | Consultant     | HF, PAD

I am on no speakers bureau

Future Therapies for Advanced HF

- Biomarkers
- Remote Monitoring
- Drugs
- Devices
- Stem Cells
- Gene Therapy
- Bioelectric Stimulation
Failed Oral DRUGS for Heart Failure

- Intravenous Inotropes-Milrinone (OPTIME)
- Calcium Sensitizer Inotrope-Levosimendan (LIDO)
- Endothelin Receptor Antagonists (RITZ)
- BNP metabolism inhibitors (OVERTURE)
- Calcium Channel Blockers (PRAISE)
- TNF antibodies (RENAISSANCE)
- Brain Natriuretic Peptide (FUSION 3)
- Vasopressin Antagonist (Tolvaptan)
- Adenosine Receptor Antagonist (PROTECT)
- ARB (Irbesartan) for Diastolic HF (I-PRESERVE)

ENTRESTO/CORLANOR

- Entresto: the most important new drug in 20 yrs
- Combination: High dose ARB, Neprolysn Inhib
- Head to Head comparison with ACEI
- 20% Relative Risk Reduction
- Reduced readmissions for HF
- New Guidelines to replace ACEI
- Corlanor-alternative to Beta Blocker for HR limit
- Also shown to reduce readmissions for HF

Factors Affecting Outcome of Drug Therapy for HF

- AGE - ELITE, HOPE
- RACE –ACEI, Beta Blockers, Hydral/Nit
- GENDER –DIG Trial, A-HFT
- ETIOLOGY-PRAISE (CCB)
- DOSE- ATLAS
- GENOMICS- BETA 2AR, eNOS, ACE I/D
- PHARMACOGENOMICS-Metoprolol
### Failed Inpatient IV Drug Trials

- DOSE-IV infusion vs Bolus diuretics
- ASCEND- BNP vs Std Care
- DAD-HF: low dose Dopamine vs diuretics
- PROTECT: Rolofyline vs std care
- CARRESS: Ultrafiltration
- RELAX: Seralaxin vs placebo
- ASTRONAUT: Aliskerin
- SMAC-HF: Hypertonic saline
- PROTECT: Synthetic BNP/vasodilator

Givertz et al J Card Fail 2013

### Future Therapies in Advanced HF
#### Reducing Readmissions

- Top Priority in HF (CMS, Payers)
- Develop Risk Scores for Readmission at D/C
- BNP < 50% of admit level → 2-3 x Readmit
- Pre-discharge one-on-one with nurse
- Telemonitoring-Weight, BP, HR
- Heart Failure Clinics-NP run
- Home visits/supervision

### Future Therapies in Advanced HF
#### Remote Monitoring

- Most sophisticated is with BiV ICDs
  - Heart Rate Variability
  - Impedance
  - Brady/Tachycardia
- A Fib
- Pulmonary Artery Pressure LA pressure
- FIT BIT-Screen Shot!
- Better trend of daily exercise
Newt can REGENERATE an entire new limb in weeks

STEM CELLs-Body’s Repair Mechanism

Capable of Endless Rejuvenation/Replication
Differentiate into all types of tissues in body

Endothelium
Bone
Fibroblasts
Adipose
Blood Cells*

Bone
Marrow
Stem Cell

Skeletal Muscle
Cardiac Myocytes
Smooth Muscle
Neural/Brain

Mechanisms of Stem Cell Therapy

INJURY
DAMAGE
IMPROVEMENT

STEM CELLS

LOCAL GENES
NATIVE REPAIR MECHANISMS
PARACRINE

Supernatant as effective as cultured cells*

*Dzau et al Nature 2002;
**Penn MS et al Cell Therapy 2001
***Marban E et al
SOURCES OF STEM CELLS: 2005

**Bone Marrow** — **Embryonic**

### Cell Therapy for Acute MI

**Bone Marrow Source**
- 17 RPC trials to date, including NIH trials*
- Small-modest sample size trials (60-120)
- Nearly all *Autologous* Bone Marrow:
  - Entire Mononuclear Cells > CD 34+ or CD 133+
  - Variable time of delivery post MI, # cells, prep
  - Variable results: EF change= + 2% (0-4\%)*
  - Best in those with lowest EF/greatest injury
- **BAMI Trial of 3,000 pt Europe** *Jeevananthum Circ 2012*

### Autologous CD 34 + Cells for Non-Ischemic Heart Failure
- 131 patients screened 2005-2006
- Average **Age= 54 yrs**: 80% males;
- EF = 25%; LVEDD= 7.0 cm; NT-BNP= 2400
- No CAD by cath
- Nuclear Scan all patients; Many had reversible Isch
- Bone Marrow source CD 34+ cells after GCSF
- Randomize 1:1 Cells vs Placebo
- Intracoronary Delivery

*Vrtovec et al Circ Res Jan 2013*
CD 34+ Stem Cells for Non-Ischemic Heart Failure:

- 5 yr follow up Results:
  - EF: increase 6% (24-30%, p=0.02)
  - 6 Min Walk: increase (344-477, p<0.001)
  - BNP: decreased 54% (2322-1011, p<0.01)
  - Total Mortality: lower (14 vs 35%, p=0.01)
  - Pump Failure Death: lower (5 vs 18%, p=0.03)
  - Sudden Death: lower (9 vs 16%, p=0.39)
  - Most benefit seen by 1 yr; persisted 5 yrs

Vetrovec et al Circ Res 2013

SOURCES OF STEM CELLS: 2017

Allogenic Mesenchymal SC’s for HF

- Any Allogenic (foreign) cell was thought to require long term immunosuppression
- Mesenchymal SCs are “Immune Privileged”
- Minimal Alloimmune(antibody) response- trials*
- Cardiotrophic: Endothelium, Cardiomyocytes, Smooth Muscle, Skel Muscle
- Equally effective as Autologous cells*
- Off-the-shelf therapy for Any Age or need

*Hare JAMA 2013
Allogeneic Mesenchymal SCs for HF
DREAM trial
- PHASE III Pivotal trial of Allogeneic MSCs
- 1700 Pt* International trial-Class II/III HF
- Both Ischemic or Non-Ischemic HF etiology
- Intramyocardial Delivery of 150 M MSCs
- Ideal 20 yo donor for all patients
- Primary End Point: Composite Event Driven
- Secondary EPs: EF, LVEDD, BNP, 6 MW

Allogeneic Mesenchymal SCs for HF
Phase III DREAM trial
- 150 Million MSCs, Randomized, Double Blind,
  Placebo Control; NOGA IM delivery
- Initial Projected Enrollment: 1700 Pts
- 1st Interim Analysis: 1200 Pts
- 2nd Interim Analysis: 600 Pts
- 3rd Interim Analysis: 400 pts-March 2017
- Trial likely stopped for Efficacy

Organ-Specific Progenitor Stem Cells
All organs likely have Resident Progenitor Cells
Generate only organ lineage-specific cells
Confirmed in Heart**, Brain*, Kidney, Lung Pancreas and Liver thus far
Heart:
- C-Kit+ cells: SCIPIO; PROMETHEUS
- Cardiospheres-CADUCEUS/ALLSTAR*
- NIH: C-Kit + Auto MSCs
Cardiac Progenitor Cells for HF: CADUCEUS Trial

- Phase IIA trial: 31 Pts < 30 days post MI, EF < 45%
- Endomyocardial Biopsy- Autologous source
- Cardiospheres: Cultured into millions cells-weeks
- Randomized 3:1 to CSP Cells vs Placebo
- Endocardial Delivery via NOGA catheter
- Results: Reduced scar mass by MRI by 24%**
  - Increased myocardial mass*(myogenesis)
  - Reduced LVESV and LVEDV
  - Improved EF by 29%

ALLSTAR Trial (Phase IIB): 274 pts-Allogeneic

Genetic Engineering
Somatic Cell Transformation

Step 1
- Reprogramming
  - Oct3,4;SOX;MFT, cMyk
  - TranscriptionFactors
- iPSCs*

Step 2
- Differentiation using small molecules/GF's
- Cardiomyocyte

*IPS: INDUCIBLE PLEURIPOTENT CELL

Unresolved Issues: Heterogeneity; Immune reactivity; Arrhythmia

Genetic Engineering of Lineage Specific Cardiopoietic SCs: C-CURE study

- Pilot of 45 patients; MI < 6 months; EF 40-50%
- Endocardial catheter delivery
- RESULTS: Decrease LVEDV, LVESV,
  - Decrease LV Scar, increase Mass
  - Increase EF % 26%
- Phase III Euro trial (CHART-250 Pts)
- Best response in Lowest EF, Largest Hearts
- Composite end points

Andre Terzic et al JACC
CATHETERS for INTRAMYOCARDIAL STEM CELL or GENE DELIVERY

NOGA CATHETER

BIOCARDIA HELIX CATHETER

NOGA Endomyocardial SC Delivery

2D

3D

SDF Gene Therapy for Heart Failure

Adventitial Catheter Delivery

Micro-infusion Catheter

Balloon atherectomy microneedle

Needle deployed with inflation

Needle reaches adventitia for infusion
Delivery of MultiStem in Post-AMI Patient
Direct Intramyocardial Delivery

RETROGRADE DELIVERY VIA CORONARY SINUS

Trial of Repeat Administrations

EF Units

6 Months 12 Months
Targeted GENE Therapy

INJURY
MYOCARD DAMAGE
Paracrine Stimulation
Native Repair
IMPROVEMENT
TARGETED GENE THERAPY

Genes for Heart Failure Therapy

SERCA-2a* S100A* Adenyl Cyclase*
Neuregulin* Heart Failure

SDF-1*
HEMAOXYGENASE ACUTE MI ENDOTHELIAL NITRIC OXIDE*.
HF-1 ALPHA

Stem Cell/Gene vs Drug Therapy

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<tr>
<td>Scalability</td>
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<tr>
<td>New Agents</td>
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Limitations of Current Approaches to Cell Therapy/Organ Regeneration

• Results of stem cell therapy for cardiac regeneration to date have shown modest benefit
• Native organ and tissue repair involves a complex interaction of many cofactors (matrix, mRNA, etc)

1. Single Cell type or agent studied
2. Single Delivery of the cell/gene/agent
   Multiple deliveries shown to have additive benefit

• Hypothesis: Continuous infusion of multiple agents may be the most effective strategy

NOVEL 3 Component Strategy for Optimizing Organ Regeneration

1. Programmable BIOELECTRIC STIMULATOR
   precise signal for local protein expression
2. Programmable MICROINFUSION PUMP
   delivery of Continuous Infusion of Regimen
3. Multi-component REGENERATIVE REGIMEN
   including: Stem Cells, Matrix, mRNA, Exosomes, and 10 pro-angiogenic or myogenic proteins

Bioelectric Stimulation to Alter Electrical Fields for Metastatic Brain Cancer

NOVOCURE
Bioelectric Stimulation for Release of Targeted Proteins

- Many Electrical Fields in body (EKG); stem cells are particularly sensitive to alterations
- 30 yrs of research defining the precise microcurrent voltage that induces local upregulation of specific targeted proteins- (Tuning a RADIO)
- Model: Fresh animal tissues are harvested; obtain baseline greatest protein expression (QPCR)
- Currently confirmed signal for 14 proteins each documented to have significant benefit organ/tissue regeneration

Effect of Surface Bioelectric Stimulation on Non-healing Ulcers-CLI

![Graph showing reduction of wound size under WMCS](image)

N=47

International Wound Journal 2014

Bioelectric Stimulator for Cardiac (Organ) Regeneration

- Miniaturized
- Implantable
- Years of Battery Life
- Programmable
- Precise Signalling
- Controls release of SDF-1, IGF, EGF, HGF, PDGF, VEGF, Activin, eNOS, VEGF, Follistatin, Tropoelastin.
- Electrical signal delivered via pacing catheter
Programmable Micro-infusion Pump for Organ Regeneration

- Small
- Implantable
- Refillable
- Programmable
- Delivers micro amts
- Corkscrew Endocard Delivery
- Catheter anchored into endocardium

Multicomponent Regimen for Organ Regeneration
(Each have been of proven benefit)

- STEM CELLS: Card Progen*, iPSCs*, UC MSC, ADRC,SKMB
- MATRIX
- EXOSOMES
- mRNA
- HYDROGELS
- STEM CELL HOMING: SDF-1
- GROWTH FACTORS: VEGF, IGF, HGF, PDGF, EGF
- FOLLISTATIN, eNOS, TROPOELASTIN, ACTIVIN

*Card Progen, iPSCs have both shown 25% reduction in FIBROSIS; NIH trial using Allogeneic MSCs in LVAD pts

RECOVERY with MCS HYPOTHESIS

IF INCREASED WALL STRESS IS THE PRIMARY STIMULUS FOR VENTRICULAR REMODELLING,
RESTING THE HEART BY TOTAL MECHANICAL UNLOADING WILL LEAD TO SUFFICIENT RECOVERY OF FUNCTION TO ALLOW DEVICE REMOVAL WITH REASONABLE, SUSTAINED, NATIVE CARDIAC FUNCTION
Reduction in Myocardial Collagen Deposition Following LVAD Therapy

Changes in Gene Expression with MCS

Beneficial Effects of LVAD Support Contractile Response to Isuprel
Surgical Delivery for Cell Therapy

Ideal opportunity at time of LVAD implant
Only clinical model to recover the tissue Tx’d

Mesenchymal Precursor Cells as Adjunctive Therapy in Recipients of Contemporary LVADs

PHASE IIA trial of Allogeneic MSCs
30 patients DT(66%) Ischemic HF onLVAD
Randomized 2:1 Cells vs Control
Epicardial Delivery of 25 M ALLO MSCs
Ideal 20 yo donor for all patients
End Point: Time off VAD with stable BP
Phase II B starting; 150 M cells

Ascheim et al Circ 2014 129:2287-96

FUTURE THERAPY OF HF

• Many new options for Advanced HF
• New Devices may become available
• Important to recognize when to REFER
• To an Advanced HF Program
• Important to Get to the Guidelines
• Target Dosing/Meds is Critical
• Need a team approach to care
• FUTURE IS OPTIMISTIC