NEW ADVANCES IN MYOCARDIAL INFARCTION THERAPY: THE REGENERATION APPROACH

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NEW ADVANCES IN MYOCARDIAL INFARCTION THERAPY: THE REGENERATION APPROACH

• Cardiovascular disease ➔ leading cause of morbidity and mortality worldwide

• Over 7 million deaths each year for AMI

• Despite advances in medical and cath-based therapy for AMI
  • 1-year mortality: 13%
  • 5-year prognosis for patients with HF: 50%

• LV systolic dysfunction:
  • major determinant of prognosis
  • associated with significant loss of cardiomyocytes
MYOCARDIAL INFARCTION

- Coronary artery occlusion
- Hypoxia Ischemia
- Heart remodeling
- Inflammation
- CMC dead
- Lack of oxygen supply
- Scar formation
- Heart failure
SC have a unique capacity to produce unaltered daughter cells (self-renewal) and to generate specialized cell types (potency).

Self-renewal:

Symmetric division:
- two stem cells
- two cells destined for differentiation

Asymmetric division:
- one stem cell and one differentiating cell
**Strategy (1):** Replication of endogenous cardiomyocytes

**Strategy (2):** Conversion of stem cells into new cardiomyocytes

*Usual Outcome:* Replacement of heart muscle with SCAR TISSUE
STEM CELL THERAPY

- Clinical trials focused on 3 main situations:
  - Acute MI (with the hope of preventing LVSD)
  - Chronic heart failure secondary to previous MI
  - DCM (non ischemic cardiomyopathy)

- Main areas of discussion:
  1. Stem cell types used in cardiac repair
  2. Methods of cell delivery in clinical practice
  3. Clinical trial evidence to date
Cell therapy in acute myocardial infarction

- Most of the trials used intracoronary delivery of BMSCs following successful stenting of the infarct-related artery.

- Surrogate markers used to assess efficacy of cell therapy:
  - Improvements in the LVEF
  - Reduction in size of scar tissue
  - Reduction in cardiac volume

- Post infarction heart failure:
  - results from ventricular remodeling processes
  - characterized by progressive expansion of the infarct area and dilation of the LV cavity
STEM CELL THERAPY IN ACUTE MI

- Major goal to reverse LV remodeling:
  - enhancement of regeneration of cardiac myocytes
  - stimulation of neovascul. within the infarct area

- Main randomized controlled trials (RCTs) published with positive findings:
  1. TOPCARE-AMI (Circulation - 2002)
  2. BOOST trial (Lancet - 2004)
  3. REPAIR-AMI trial (EJM - 2006)
  4. FINCELL (Eur Heart J - 2008)
CELL THERAPY IN ACUTE MI

RCTs with neutral findings:

- LEUVEN-AMI study: No changes in global LVEF after BMSC infusion
  
- ASTAMI trial: No significant effect on the LVEF, LV volumes, or infarct size
  
- HEBE trial: No changes in global or regional LV systolic function after BMSC therapy

1 Janssens et al. Lancet 2006;367:113–21
3 Alexander Hirsch et al. Eur Heart J 2010
RCTs OF INTRACORONARY BMSC THERAPY AFTER ACUTE MI

<table>
<thead>
<tr>
<th>Study name (ref)</th>
<th>Date published</th>
<th>$n$</th>
<th>Days after AMI</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOPCARE-AMI$^{41}$</td>
<td>2002</td>
<td>59</td>
<td>$4.3 \pm 1.5$</td>
<td>Improvement in global LVEF from $51.6 \pm 9.6%$ to $60.1 \pm 8.6%$ ($P = 0.003$) at 4 months</td>
</tr>
<tr>
<td>BOOST$^{42}$</td>
<td>2004</td>
<td>60</td>
<td>$5.1 \pm 1.3$</td>
<td>Improvement in global LVEF at 6 months but effect was only maintained in large infarcts at long-term follow-up</td>
</tr>
<tr>
<td>REPAIR-AMI$^{43}$</td>
<td>2006</td>
<td>187</td>
<td>3–6</td>
<td>Improvement in the LVEF at 4 months by 2.5% above baseline</td>
</tr>
<tr>
<td>ASTAMI$^{46}$</td>
<td>2006</td>
<td>97</td>
<td>$6 \pm 1$</td>
<td>No change in the LVEF at 6 months</td>
</tr>
<tr>
<td>LEUVEN-AMI$^{45}$</td>
<td>2006</td>
<td>66</td>
<td>1</td>
<td>No change in global LVEF at 4 months but there was improvement in regional contractility and infarct size in patients with the largest infarcts</td>
</tr>
<tr>
<td>FINCELL$^{44}$</td>
<td>2008</td>
<td>77</td>
<td>3</td>
<td>Improvement in the LVEF at 6 months by 5% above baseline</td>
</tr>
<tr>
<td>HEBE$^{47}$</td>
<td>2010</td>
<td>200</td>
<td>3–8</td>
<td>No change in global LVEF at 4-month follow-up</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; BMSC, bone marrow stem cells; $n$, number of patients; LVEF, left ventricular ejection fraction.
STEM CELL THERAPY IN ACUTE MI

Reasons for the inconsistent findings:

1. Variations in the number of cells delivered
2. Timing of delivery after AMI
3. Differences in the cell isolation protocol
4. Others
## SECOND GENERATION STEM CELL THERAPY

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Design</th>
<th>Type of cells</th>
<th>Delivery route</th>
<th>Clinical setting</th>
<th>Follow-up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartunek et al.⁹⁵⁵</td>
<td>47</td>
<td>Multicenter, randomized 2:1</td>
<td>Autologous bone marrow derived cardiopoietic MSCs</td>
<td>Endomyocardial injection</td>
<td>Chronic ischemic heart failure (LVEF 15%-40%)</td>
<td>Safety 2 yr</td>
<td>Feasible and safe</td>
</tr>
<tr>
<td>(C-CURE)</td>
<td></td>
<td>(cells vs standard of care)</td>
<td></td>
<td></td>
<td></td>
<td>Efficacy 6 mo</td>
<td>↓ LVEF</td>
</tr>
<tr>
<td>Bolli et al.¹¹¹⁹</td>
<td>23</td>
<td>Unicenter, randomized 2:1</td>
<td>Autologous c-kit+/lin- CSCs</td>
<td>Intra-coronary infusion</td>
<td>Chronic ischemic heart failure (LVEF ≤ 40% four months post CABG)</td>
<td>12 mo</td>
<td>Feasible and safe</td>
</tr>
<tr>
<td>(SCIPIO)</td>
<td></td>
<td>(cells vs standard of care)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ LVEF</td>
</tr>
<tr>
<td>Malliaras et al.¹¹²²</td>
<td>25</td>
<td>Two centers, randomized 2:1</td>
<td>Autologous CDCs</td>
<td>Intra-coronary infusion</td>
<td>Chronic ischemic heart failure (1.5-3 mo after MI)</td>
<td>12 mo</td>
<td>Feasible and safe</td>
</tr>
<tr>
<td>(CADUCEUS)</td>
<td></td>
<td>(cells vs standard of care)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ Infarct size</td>
</tr>
<tr>
<td>Hare et al.¹¹¹⁴</td>
<td>30</td>
<td>Multicenter, randomized 1:1</td>
<td>Three different doses of autologous or allogeneic bone</td>
<td>Endomyocardial injection</td>
<td>Chronic ischemic heart failure (LVEF ≤ 50%)</td>
<td>12 mo</td>
<td>Feasible and safe</td>
</tr>
<tr>
<td>(POSEIDON)</td>
<td></td>
<td>(autologous vs allogeneic cells)</td>
<td>marrow derived MSCs</td>
<td></td>
<td></td>
<td></td>
<td>≈ LVEF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Autologous ↑ 6-min walk distance and QoL</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Allogeneic ↓ LVEDV</td>
</tr>
</tbody>
</table>

↑: Indicates increased; ↓: Indicates decreased; ≈: Indicates no change; MI: Myocardial infarction; MSCs: Mesenchymal stem cells; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end-systolic volume; QoL: Quality of life; CSCs: Cardiac stem cells; CABG: Coronary artery by-pass graft; CDCs: Cardiosphere-derived cells; LVEDV: Left ventricular end-systolic volume.
CURRENT ACCESS ROUTES FOR CELL THERAPY

- Transvascular Delivery
- Intracoronary Perfusion
- Epicardial Delivery
- Endocardial Delivery
Cell Therapy

- Unselected cells
- Purified/selected cells
- Cells with Materials

Cell Free Therapy

- Acellular Biomaterials
- Small Molecules
- RNA Therapy
- Growth Factors
- Proteins
THE TISSUE ENGINEERING TRIAD

Biomaterials

- Cell migration
- Cell engraftment
- Cell behaviour

Tissue engineering
- Protein protection
- Controlled release
- Reduced side effects

Stem Cells
- Cell differentiation
- Cell viability

Growth factors
PRINCIPAL BENEFITS OF BIOMATERIALS

- **Cell Migration and Tissue Regeneration:** Reproduce tissue environment, encourage tissue regrowth
- **Encapsulated Cells:** Increase viable cell retention, facilitate paracrine effect
- **Matrix Support:** Improve cell behavior, 3D environment
- **Controlled Release Reservoir:** Protect degradation, prolonged delivery, reduce side effects
TYPES OF DRUG DELIVERY SYSTEMS MADE OF BIOMATERIALS

- Nanofibers
- Hydrogels
- Liposomes
- Nano and micro-particles
Left Ventricular Restraint  In Vitro Engineered Tissue  In Situ Engineered Tissue
Rat model of myocardial infarction (WKY, N=20)
Membranes 8 weeks following AMI

H&E

(C-Troponin, 40x)

(Phalloidin, 20x)
ADVANCED DELIVERY

Towards Advanced Delivery

1 Localized Therapy
2 Nanoparticle Encapsulation
3 Minimally Invasive Delivery
4 Multimodal Approaches
FUTURE CONCEPTS FOR REGENERATIVE THERAPIES

**Transplantation**
- cardiomyocytes
- ESCs/iPSCs
- cardiac progenitors

**Stimulation of resident cell sources**
- Thyomisin β4
- NRG 1, p38 MAPK, P, miRNA, etc.
- cardiac progenitors
- cardiomyocytes

**Differentiation/proliferation**
- cell-cycle re-entry

**Direct reprogramming**
- Mesp1, Ets2
- Gata4, Mef2c, Tbx5, (Hand2), etc., miRNA

**Tissue engineering**
- implantation

**Fibroblasts**
- cardiac progenitors
- cardiomyocytes
CONCLUSIONS

- Past decade has seen an explosion in clinical studies investigating the safety and efficacy of Cell therapy for heart diseases.
- Safety of SC therapy has been demonstrated uniformly in the vast majority of the studies.
- Beneficial effects of cell therapy have been not fully demonstrated: AMI, chronic ischemic HF and DCM.
- New technologies and advances also led to ”Second Generation SC”, Protein (Growth factors) and Biomaterials therapy showing promising effects.
- Need for larger RCTs with longer term follow-up assessing morbidity and mortality as primary outcome measures.