Transendocardial Mesenchymal Stem Cells and Mononuclear Bone Marrow Cells for Ischemic Cardiomyopathy: The TAC-HFT Randomized Trial

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University of Miami Miller School of Medicine
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Background

• BMCs and BM derived MSCs are lead candidates for cell therapy for ischemic cardiomyopathy (ICM).
• The safety and efficacy of intramyocardial BMCs and MSCs have not been fully established.
Objectives

• To demonstrate the safety of transendocardial stem cell injection (TESI) with autologous MSCs and BMCs in patients with ICM.

• To assess prespecified outcomes of efficacy.
Methods

• A phase I/II randomized blinded placebo-controlled study.

• **Setting:** A US tertiary-care referral hospital – University of Miami Miller School of Medicine / University of Miami Hospital.

• **Patients:** 65 with LV dysfunction due to ICM.

• **Interventions:** 200 million cells or placebo injected into 10 LV sites using the Bioccardia Helical Infusion Catheter.

http://clinicaltrials.gov/ct2/show/NCT00768066
Study Flow Chart

Assessed for Eligibility (n=97)

- Excluded (n=32)
  - Not eligible (n=14)
  - Declined to participate (n=4)
  - Other reasons (n=14)

Randomized 1:1 to Group (n=65)

Randomized 2:1 MSCs or Placebo (n=33)
- MSCs (n=22)*
- Placebo (n=11)

Randomized 2:1 BMCs or Placebo (n=32)
- BMCs (n=22)*
- Placebo (n=10)

*3 MSC patients did not receive MSCs:
- Withdrew consent (n=2)
- Cell processing failure (n=1)

*3 BMC patients did not receive BMCs:
- Withdrew consent (n=2)
- Became ineligible (n=1)
Outcomes

• SAFETY
  • 30 Day safety
  • 1 Year safety

• EFFICACY
  • 6-minute walk test
  • Peak VO2
  • Minnesota Living with Heart Failure Questionnaire
  • NYHA
  • Cardiac MRI and CT for Global and Regional analysis.
<table>
<thead>
<tr>
<th></th>
<th>Group: MSC/Placebo</th>
<th>Group: BMC/Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MSCs (N=19)</td>
<td>Placebo (N=11)</td>
</tr>
<tr>
<td></td>
<td>BMCs (N=19)</td>
<td>Placebo (N=10)</td>
</tr>
<tr>
<td>Male sex</td>
<td>18 (94.7%)</td>
<td>10 (90.9%)</td>
</tr>
<tr>
<td></td>
<td>17 (89.5%)</td>
<td>10 (100.0%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.1 (10.6)</td>
<td>60.0 (12.0)</td>
</tr>
<tr>
<td></td>
<td>61.1 (8.4)</td>
<td>61.3 (9.0)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>35.8 (8.5)</td>
<td>31.6 (10.0)</td>
</tr>
<tr>
<td></td>
<td>36.3 (11.1)</td>
<td>34.4 (9.5)</td>
</tr>
<tr>
<td>Hx of Coronary Interventions</td>
<td>19 (100.0%)</td>
<td>10 (90.9%)</td>
</tr>
<tr>
<td></td>
<td>18 (94.7%)</td>
<td>10 (100.0%)</td>
</tr>
<tr>
<td>Hx of Hypertension</td>
<td>12 (63.2%)</td>
<td>6 (54.5%)</td>
</tr>
<tr>
<td></td>
<td>12 (63.2%)</td>
<td>10 (100.0%)</td>
</tr>
<tr>
<td>History of Diabetes</td>
<td>3 (15.8%)</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td></td>
<td>4 (21.1%)</td>
<td>4 (40.0%)</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>5 (26.3%)</td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td></td>
<td>5 (26.3%)</td>
<td>2 (25.0%)</td>
</tr>
<tr>
<td>Class II</td>
<td>12 (63.2%)</td>
<td>5 (50.0%)</td>
</tr>
<tr>
<td></td>
<td>10 (52.6%)</td>
<td>5 (62.5%)</td>
</tr>
<tr>
<td>Class III</td>
<td>2 (10.5%)</td>
<td>3 (30.0%)</td>
</tr>
<tr>
<td></td>
<td>4 (21.1%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>6MWT</td>
<td>415.3 (67.9)</td>
<td>388.5 (69.0)</td>
</tr>
<tr>
<td></td>
<td>399.6 (95.0)</td>
<td>387.8 (47.8)</td>
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<tr>
<td>Peak VO2 (mL/kg/min)</td>
<td>18.8 (3.8)</td>
<td>14.5 (4.5)</td>
</tr>
<tr>
<td></td>
<td>17.3 (4.4)</td>
<td>14.6 (7.0)</td>
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<tr>
<td>% Predicted FEV₁</td>
<td>86.2 (15.7)</td>
<td>77.0 (14.2)</td>
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<tr>
<td></td>
<td>83.2 (23.2)</td>
<td>81.4 (25.8)</td>
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<tr>
<td>MLHFQ Total Score</td>
<td>28.4 (22.8)</td>
<td>18.9 (15.0)</td>
</tr>
<tr>
<td></td>
<td>29.5 (25.8)</td>
<td>44.9 (24.9)</td>
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SAFETY
Transendocardial injection of both cell types was not associated with an increased risk of adverse side effects, nor was ectopic tissue formation detected.

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<tr>
<td></td>
<td>Placebo (N=11)</td>
<td>Placebo (N=10)</td>
</tr>
<tr>
<td><strong>Primary Endpoint: Incidence of TE-SAE, n (%)</strong></td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td># of AEs</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td># of AEs/Patient, median (range)</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>Incidence of AE, n (%)</td>
<td>6 (31.6%)</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td># of SAEs</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td># of SAEs/Patient, median (range)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Incidence of SAE, n (%)</td>
<td>2 (10.5%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Major Adverse Cardiac Event, n (%)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>---</td>
<td>---</td>
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<tr>
<td>Ectopic Tissue Formation</td>
<td>---</td>
<td>---</td>
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</tbody>
</table>
Incidence of AE/SAE by day 30 and 365 Post-TESI

By Day 30
- MSC
- Placebo
- BMC
- Placebo

By Day 365
- MSCs
- Placebo
- BMC
- Placebo

Incidence (%)
Post Procedure Cardiac Injury Markers

![Graph showing CK-MB and Troponin I levels over time for different groups.](image-url)
EFFICACY
Impact of Cell Therapy on QOL

*p<0.05, **p<0.01

Time Post-TESI

- MSCs
- BMCs
- Placebo

*Total Score*
Impact of Cell Therapy on Functional Capacity

*\( p < 0.05 \), **\( p < 0.01 \)

Distance Walked in 6-Minutes (m)

![Graph showing the impact of cell therapy on functional capacity. The graph compares the distance walked in 6 minutes before and after treatment with different types of cell therapy: MSCs, BMCs, and Placebo. The graph includes error bars and annotations for statistical significance.](image)
Impact of Cell Therapy on Infarct Size

<table>
<thead>
<tr>
<th>Time Post-TESI</th>
<th>MSCs</th>
<th>BMCs</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3M</td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6M</td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12M</td>
<td></td>
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</tbody>
</table>

*Scar size (DE): 30.85g
**Scar size (DE): 32.44g
***Scar size (DE): 30.85g

*p<0.05, **p<0.01, ***p<0.001
Scar size reduction is accompanied with increase in viable tissue only in the MSCs group.

MSC vs Placebo: p=0.05

p=0.005 8.4%
Impact of Cell Therapy on Regional Myocardial Function – Tissue Tagging

*<0.05, **<0.01

Baseline

Peak Ecc
White arrow: -2.2

Baseline

1 year

Peak Ecc
White arrow: -17.3
CINE Tagging MRI depicts Improvement in Regional Function after MSCs

Baseline peak Ecc

Peak Ecc
White arrow: -2.2

1 year peak Ecc

Peak Ecc
White arrow: -17.3
Impact of scar reduction on quality of life

Linear regression for all patients: \( r=0.33 \) (\( p=0.0385 \). Pearson correlation for MSCs was 0.53 (\( P=0.0738 \)), BMCs was 0.16 (\( P=0.57 \)) and Placebo 0.32. MSC vs. BMC: \( p=0.0070 \), MSC vs. placebo: \( p=0.01 \), BMC vs. Placebo: \( p=0.92 \)
Impact of Cell Therapy on EF and LV Volumes

**LVEF**

- MSCs (n=16)
- BMCs (n=16)
- Placebo (n=17)

**ESV**

- MSCs (n=16)
- BMCs (n=16)
- Placebo (n=17)

**EDV**

- MSCs (n=16)
- BMCs (n=16)
- Placebo (n=17)
Summary

• TESI with autologous MSCs or BMCs appeared to be safe in patients with chronic ICM and LV dysfunction

• MSCs
  – Improved MHFQ and 6MWT
  – Decreased scar size
  – Improved regional wall motion at site of cell injection

• BMCs
  – Improved MHFQ

• Exploratory evaluation: scar reduction correlates with improved QOL

• EF and LV volumes did not improve with cell therapy
Conclusion

• The safety profile and the findings of scar reduction, improved quality of life and functional capacity provide the basis for larger studies to provide definitive assessment of safety and efficacy of this new therapeutic approach.

• Study limitations: small sample size and multiple endpoint testing.
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Available at www.jama.com

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Thank you