Stem cell therapy in end-stage ischaemic heart failure: a catheter-based therapeutic strategy targeting myocardial viability

Emerson C. Perin* and Guilherme V. Silva

Department of Adult Cardiology, Texas Heart Institute, St. Luke’s Episcopal Hospital, 6624 Fannin, Suite 2220, Houston, TX 77030, USA

Recent evidence that the adult heart can repair itself through the proliferation of cardiac precursor cells and the recruitment and engraftment of bone marrow-derived precursor cells has stimulated interest in stem cell therapy for cardiac diseases. Although preclinical studies have shown the efficacy of stem cell treatment, numerous controversies exist, and many basic questions still await answers. Meanwhile, clinical trials of stem cell therapy continue to advance. Our group has focused on using stem cells to treat patients with end-stage ischaemic heart failure who are ineligible for surgical or percutaneous revascularization. The preliminary results of the phase I trial are encouraging but need to be reproduced before larger randomized trials can be attempted. This review covers some of the most important clinical developments in targeted, transendocardially delivered stem cell therapy for end-stage ischaemic heart failure.

KEYWORDS
Stem cell therapy; Cardiac; Ischaemic heart failure; Myocardial viability; Transendocardial stem cell delivery; Bone marrow-derived mononuclear cells; Electromechanical mapping

Introduction

Until recently, cardiologists believed that the heart lacked the capacity to renew itself. However, new insights into the mechanisms of cardiac repair have provided evidence that the adult heart can repair itself through intricate mechanisms that include proliferation of cardiac precursor cells and recruitment and engraftment of bone marrow-derived precursor cells. These insights, in turn, have sparked strong interest in the field of stem cell therapy for cardiac diseases. The idea of using stem cells to repair or replace the myocardium has been met with both enthusiasm and skepticism. Despite solid preclinical evidence of the efficacy of stem cell treatment, numerous controversies exist, and many basic questions still await answers. Meanwhile, clinical trials of stem cell therapy continue to advance.

Along with other investigators, our group at the Texas Heart Institute at St. Luke’s Episcopal Hospital has focused on using stem cells to treat the most challenging population in cardiology: patients with end-stage ischaemic heart failure who have no options for surgical or percutaneous revascularization. The chosen stem cell delivery mode for this patient population is the transendocardial route. The preliminary results of the phase I trial offer significant hope that stem cell therapy will become an important clinical tool. The present review covers some of the most important clinical developments in targeted, transendocardially delivered stem cell therapy for end-stage ischaemic heart failure.

Bone marrow-derived mononuclear cells

The bone marrow is a complex organ that comprises haematopoietic progenitor cells, osteocytes and osteoblasts, and supporting mesenchymal cells (stromal cells). Adult bone marrow-derived stem cells are the most widely used cell type in cardiac stem cell therapy. Bone marrow-derived stem cells are aspirated from the patient’s iliac crest with the aid of local anaesthesia.
After being isolated by means of Ficoll density centrifugation, the mononuclear sub-fraction of the aspirate is filtered through a 100 μm nylon mesh to remove cell aggregates or bone spicules, washed several times in phosphate-buffered saline solution, and then used immediately for therapy.

This separation process results in a heterogeneous subset, termed autologous bone marrow-derived mononuclear cells (ABMMNCs), which include small amounts of stromal or mesenchymal stem cells, haematopoietic progenitor cells, endothelial progenitor cells, and more committed cell lineages such as natural killer lymphocytes, T lymphocytes, and B lymphocytes. This approach has the advantage of being simple and less technically challenging because cell culture is not required. Cells are not manipulated, and the risk of infection is small. Whereas no specific single (and possibly more potent) cell type is administered in larger quantities, multiple cell lineages are left to interact with themselves and with the milieu in which they are placed.

Transendocardial stem cell injections guided by electromechanical mapping: targeting electrical viability

Stem cells may be injected in a targeted fashion or may be introduced through the vascular system, in which case their ultimate location is determined by homing signals. The targeted approach not only delivers cell therapy precisely into the injured area, but also takes into account the characteristics of the underlying tissue.

Three-dimensional left ventricular (LV) endocardial maps or electromechanical maps (EMMs) are utilized to navigate an injection catheter and characterize underlying tissue for targeting injections (Figure 1). These maps are created with the aid of non-fluoroscopic magnetic guidance.4 In brief, a triangular magnetic pad, positioned beneath the patient, generates ultra-low magnetic fields (10⁻⁵ to 10⁻⁶ T). The intersection of those magnetic fields with a sensor just proximal to the deflectable tip of a 7F mapping catheter, helps determine the real-time location and orientation of the catheter tip inside the LV. A three-dimensional endocardial ‘shell’ is constructed by acquiring a series of points at multiple locations on the endocardial surface allowing precise regional cell delivery into the ischaemic area.

In addition, the injection catheter incorporates electrodes that measure endocardial electrical signals (unipolar or bipolar voltage). Voltage values are assigned to each point acquired during LV mapping, and an electrical map is constructed concurrently with the mechanical map. Several clinical studies have validated the concept of electrical viability: measurement of endocardial voltage potentials provides a reliable and accurate assessment of myocardial viability.5–11 In general, a unipolar voltage (UniV) of <4.5 mV should represent non-viable myocardium with nearly 100% certainty. Also, a UniV of 4.5–8.4 mV corresponds to variable degrees of viability, which are compatible with the relatively non-uniform nature of myocardial necrosis. A UniV >6.9 mV will identify viable myocardial segments by means of delayed hyperenhancement magnetic resonance imaging with 93% sensitivity and 88% specificity.10 Thus, EMM-guided transendocardial injections integrate anatomic precision with detailed tissue characterization.

The value of targeted cell therapy is unclear. Injecting ABMMNCs into non-vascularized tissues such as myocardial scar tissue compromises stem cell survival. This has been confirmed by Agbulut et al.,12 who found that injection of bone marrow-derived CD133-positive cells into scarred myocardium was associated with less engraftment (and therefore less efficacy) than was injection of skeletal myoblasts. Therefore, in our initial clinical experience with transendocardial injection of ABMMNCs, described below, we targeted viable myocardium by injecting the only tissue that had a voltage >6.9 mV.

Clinical trials

Preliminary clinical evidence supports the efficacy of transendocardial injections of ABMMNCs in treating ischaemic heart disease. Moreover, all of the evidence appears to substantiate its safety.

Tse et al.13 transendocardially injected ABMMNCs into eight patients with severe ischaemic heart disease and preserved LV function, as indicated by the LV ejection fraction (LVEF). After 3 months of follow-up study, these researchers observed an improvement in symptomatology and myocardial perfusion. Cardiac magnetic
resonance imaging showed improved perfusion and contractility in the ischaemic region.

Fuchs et al. conducted a clinical feasibility study of transendocardial delivery of filtered, unfractionated autologous bone marrow-derived (not mononuclear) cells in 10 patients with severe chronic, symptomatic myocardial ischaemia not amenable to conventional revascularization. Twelve injections (0.2 mL each) were administered into ischaemic, non-infarcted myocardium that was pre-identified with single-photon emission computed tomography (SPECT) perfusion imaging. The patients had no serious adverse effects (i.e. arrhythmia, infection, myocardial inflammation, or increased scar formation). The treadmill exercise duration (available for nine patients) did not change significantly (391 ± 155 vs. 485 ± 198 s; P = 0.11), but there was improvement in Canadian Cardiovascular Society angina scores (3.1 ± 0.3 vs. 2.0 ± 0.94; P = 0.001) and in stress scores involving segments within the injected regions (2.1 ± 0.8 vs. 1.6 ± 0.8; P < 0.001).

Our group performed the first clinical trial in which transendocardially injected ABMMNCs were used to treat end-stage ischaemic heart failure patients with severe systolic dysfunction. We have published the results of 2- and 4-month non-invasive and invasive follow-up studies, as well as 6- and 12-month follow-up studies. The trial involved 21 patients, the first 14 of whom comprised the treatment group and the last 7 of whom formed the control group. Baseline evaluations included complete clinical and laboratory tests, exercise stress (ramp treadmill) studies, two-dimensional Doppler echocardiography, SPECT perfusion scanning, and 24 h Holter monitoring. Bone marrow-derived mononuclear cells were harvested, isolated, washed, and resuspended in saline for injection by a NOGA catheter (15 injections of 0.2 cc each, totalling 30 × 10^6 cells per patient). Electromechanical mapping was performed to identify viable myocardium (UnIV > 6.9 mV), and the results were integrated with the SPECT findings to define the treatment area. Only points with preserved viability were injected.

All patients underwent non-invasive follow-up tests at 2 months. The treatment group also underwent invasive studies at 4 months, using standard protocols and the same procedures as at baseline. The demographic and exercise test variables did not differ significantly between the treatment and control groups. No procedural complications occurred, and no periprocedural arrhythmias were identified. At 2 months, quantitative SPECT analysis showed that when compared with the control patients, the treatment group had a significant reduction in the total reversible defect (P = 0.02). At 4 months, the LVEF had improved from a baseline of 20–29% (P = 0.003) in the treated patients, and the end-systolic volume was reduced (P = 0.03).

Electromechanical mapping revealed significant mechanical improvement of the injected segments (P < 0.0005). More important, the significant improvement seen at 2 and 4 months was maintained at 6 and 12 months. In addition, the treated group’s exercise capacity improved significantly (Table 1).

Thus, overall transendocardial injection of ABMMNCs was safe and preliminarily effective. This was the first time objective evidence of perfusional and functional improvement had been seen in patients with severe ischaemic heart failure treated solely with cell therapy.

Lessons learned from a phase I trial: insights into transendocardial delivery strategies and the mechanism of action of ABMMNCs

Many clinical aspects of cardiac cell therapy, such as the timing of improvement, are still uncertain. To further clarify this issue in our study, the treatment group had baseline and weekly post-treatment assessments of New York Heart Association (NYHA) functional status, CCS anginal class, and LVEF by means of two-dimensional echocardiography (Simpson’s method) for up to 10 weeks (unpublished data). The significant improvement in NYHA occurred at 4 weeks (P = 0.0002) and in CCS status at 7 weeks (P = 0.000006). A significant improvement in LVEF was also observed between 6 and 8 weeks (P = 0.04).

These data suggest that symptomatic, functional, and myocardial perfusional improvements occur during the second month of follow-up after ABMMNC transplantation. Several mechanistic aspects remain unclear, and the ideal transendocardial delivery strategy is undefined. In our treated patients, we studied the possible effects of injection-area size, cell density, and specific cell type on improvement in myocardial ischaemia. The concentration of each specific ABMMNC phenotype (10^5 cells/mm^3), the size of the injected myocardial area (mm^2), and the bone-marrow cell density (10^5 cells/mm^3) were calculated for every patient. The result was then correlated with the reduction in the total reversible defect on quantitative SPECT (at baseline vs. 24 weeks) using exact Pearson product–moment correlation (non-published data). Monocyte, B-cell, haematopoietic progenitor cell, and early haematopoietic progenitor cell subpopulations correlated with an improvement in reversible perfusion defects at 6 months (Table 2). There was a significant reduction in the total reversible defect area in patients with smaller (less widespread) injected areas (r = 0.7; P < 0.02) and a higher cell density (r = 0.6; P < 0.006).

It would be premature to attribute the functional improvement seen in this study exclusively to ABMMNCs. However, our recent description of the post-mortem study of one of our patients who received ABMMNCs may provide further mechanistic insight into the tissue effects of ABMMNCs. This patient died of a neurological event 11 months after undergoing cell injections. At autopsy, no abnormal or disorganized tissue growth, abnormal vascular growth, or enhanced inflammatory reaction was observed. Histological and immunohistochemical findings from infarcted areas of the anterolateral ventricular wall (which had received bone marrow cell injections) were compared with (a) findings from within the interventricular septum (which had normal perfusion in its central region and received no cell therapy) and (b) findings from the previously...
Table 1  Comparison of clinical values for the treatment and control groups at baseline, 2, 6, and 12 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>2 months</th>
<th>6 months</th>
<th>12 months</th>
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<tbody>
<tr>
<td></td>
<td>Rx</td>
<td>Control</td>
<td>Rx</td>
<td>Control</td>
<td>Rx</td>
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<tr>
<td>SPECT</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total reversible defect (%)</td>
<td>14.8 ± 14.5</td>
<td>20 ± 25.4</td>
<td>4.45 ± 11.5</td>
<td>37 ± 38.4</td>
<td>8.8 ± 9</td>
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<tr>
<td>Total fixed defect (50%) (%)</td>
<td>42.6 ± 10.3</td>
<td>38 ± 12</td>
<td>39.8 ± 6.9</td>
<td>39.1 ± 11.2</td>
<td>38 ± 6.7</td>
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<td>Ramp treadmill test</td>
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<td></td>
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<tr>
<td>VO₂ max (mL/kg/min)</td>
<td>17.3 ± 8</td>
<td>17.5 ± 6.7</td>
<td>23.2 ± 8</td>
<td>18.3 ± 9.6</td>
<td>24.2 ± 7</td>
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<tr>
<td>METS</td>
<td>5.0 ± 2.3</td>
<td>5.0 ± 1.91</td>
<td>6.6 ± 2.3</td>
<td>5.2 ± 2.7</td>
<td>7.2 ± 2.4</td>
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<tr>
<td>LVEF</td>
<td>30 ± 6</td>
<td>37 ± 14</td>
<td>37 ± 6</td>
<td>27 ± 6</td>
<td>30 ± 10</td>
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<td>Functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NYHA</td>
<td>2.2 ± 0.9</td>
<td>2.7 ± 0.8</td>
<td>1.5 ± 0.5</td>
<td>2.4 ± 1.0</td>
<td>1.3 ± 0.6</td>
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<tr>
<td>CCSAS</td>
<td>2.6 ± 0.8</td>
<td>2.9 ± 1.0</td>
<td>1.8 ± 0.6</td>
<td>2.5 ± 0.8</td>
<td>1.4 ± 0.5</td>
</tr>
<tr>
<td>PVCs (n)</td>
<td>2507 ± 6243</td>
<td>672 ± 1085</td>
<td>901 ± 1236</td>
<td>2034 ± 4528</td>
<td>3902 ± 8267</td>
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<tr>
<td>dQRS (ms)</td>
<td>136 ± 15</td>
<td>145 ± 61</td>
<td>145.9 ± 25</td>
<td>130 ± 27</td>
<td>144.8 ± 25</td>
</tr>
<tr>
<td>LAS 40 (ms)</td>
<td>50 ± 24</td>
<td>70 ± 76</td>
<td>54 ± 33</td>
<td>48 ± 20</td>
<td>25 ± 25</td>
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<tr>
<td>RMS 40 (µV)</td>
<td>22.2 ± 22</td>
<td>23.3 ± 23</td>
<td>23.3 ± 19</td>
<td>24.6 ± 28</td>
<td>25 ± 25</td>
</tr>
</tbody>
</table>

PCCAS, Canadian Cardiovascular Society Angina Score; dQRS, filtered QRS duration; LAS 40, duration of terminal low-amplitude signal <40 mV; LVEF, left ventricular ejection fraction; METS, metabolic equivalents; PVCs, premature ventricular contractions; RMS 40, root mean square voltage in the terminal 40 ms of the QRS complex; Rx, treatment; VO₂ max, maximal rate of oxygen consumption. Reprinted from Perin et al. Circulation 2004;110(Suppl. II):213–218 with permission.16

*P-value for comparisons between the treatment and control groups, as assessed by ANOVA, relating to treatment over time.
infarced inferoposterior ventricular wall (which had extensive scarring and no cell therapy). Some intriguing findings were noted:

(a) The cell-treated, infarcted areas had a higher capillary density than did the non-treated, infarcted areas of the heart.

(b) Proliferation of smooth muscle α-actin-positive pericytes and mural cells was noted exclusively in the cell-treated areas.

(c) These pericytes and mural cells expressed specific cardiomyocyte proteins (Figure 2).

The histological findings in the cell-treated wall may have reflected an intense neo-angiogenic process. The angiogenesis literature clearly shows that pericytes are essential for achieving a long-lasting physiologic angiogenic process. In our postmortem study, the cell-injected wall had marked hyperplasia of pericytes and mural cells. The observed hypertrophic pericytes, though located in the vascular wall, expressed specific myocardial proteins and were distant from the vessel walls, suggesting detachment. Migrated pericytes and mural cells were found in the adjacent tissue (in the vicinity of cardiomyocytes), either in isolation or in small cell clumps. Closer to cardiomyocytes, the expression of myocardial proteins was enhanced, yielding brighter immunostaining throughout the whole cytoplasm. Within the posterior wall, none of these findings was seen, and small blood vessels could only rarely be found.

In our study, the findings that were consistent with an angiogenic process associated with cell therapy were similar to those seen in most preclinical studies involving models of chronic myocardial ischaemia.

Conclusion

ABMMNCs have an enormous potential to help millions of patients with end-stage ischaemic heart failure who have no other therapeutic options. In delivering ABMMNCs to these patients, targeting of viable myocardium is probably the most precise strategy. The science behind stem cell therapy for ischaemic heart disease is allied to a great unmet clinical need, providing clinical researchers with enough confidence to pursue clinical trials. However, the results of initial phase I trials regarding safety and efficacy endpoints need to be reproduced before larger randomized trials are undertaken.

Conflict of interest: E.C.P. is consultant and speaker for Cordis and received grants to fund research fellows.

References


