Safety and Efficacy of Ixmyelocel-T
An Expanded, Autologous Multi-Cellular Therapy, in Dilated Cardiomyopathy

Timothy D. Henry, Jay H. Traverse, Baron L. Hammon, Cara A. East, Brian Bruckner, Ann E. Remmers, David Recker, David A. Bull, Amit N. Patel

**Rationale:** Ixmyelocel-T is associated with a wide range of biological activities relevant to tissue repair and regeneration.

**Objective:** To evaluate the safety and efficacy of ixmyelocel-T in 2 prospective randomized phase 2A Trials administered via minithoracotomy or intramyocardial catheter injections in patients with dilated cardiomyopathy (DCM) stratified by ischemic or nonischemic status.

**Methods and Results:** In IMPACT-DCM, patients were randomized to either ixmyelocel-T or standard-of-care control in a 3:1 ratio (n=39); ixmyelocel-T was administered intramyocardially via minithoracotomy. In Catheter-DCM, patients were randomized to either ixmyelocel-T or standard of care control in a 2:1 ratio (n=22); ixmyelocel-T was administered intramyocardially using the NOGA Myostar catheter. Only patients randomized to ixmyelocel-T underwent bone marrow aspiration and injections. In the 2 studies, a total of 61 patients were randomized, and 59 were treated or received standard of care. Fewer ischemic patients treated with ixmyelocel-T experienced a major adverse cardiovascular event during follow-up when compared with control patients. A similar benefit was not seen in the nonischemic patients. Heart failure exacerbation was the most common major adverse cardiovascular event. Ixmyelocel-T treatment was associated with improved New York Heart Association class, 6-minute walk distance, and Minnesota Living with Heart Failure Questionnaire scores in the ischemic population relative to control; a similar trend was not observed in the nonischemic population.

**Conclusions:** Intramyocardial injection with ixmyelocel-T reduces major adverse cardiovascular event and improves symptoms in patients with ischemic DCM but not in patients with nonischemic DCM. (Circ Res. 2014;115:730-737.)

**Key Words:** cardiomyopathy, dilated ■ clinical trial ■ heart failure ■ stem cell

Heart failure (HF) remains a major public health burden, affecting ≈5.1 million adults in the United States. Approximately 50% of patients diagnosed with HF will die within 5 years, and the prevalence is growing. Improvements in the pharmacological and surgical management of patients with cardiovascular disease have improved leading to increased survival, which in turn has led to an increasingly elderly patient population more likely to develop worsening, irreversible HF.1–2 Despite optimal medical therapy, ventricular assist devices and cardiac transplantation are frequently the only remaining options for these patients when medication and device therapies fail.3 Cell therapy has emerged as an attractive alternative therapy, given the positive preclinical results and encouraging early clinical trial results.4–7 Recently, the National Heart, Lung, and Blood Institute–sponsored FOCUS trial demonstrated no overall improvement in maximal oxygen consumption or end-systolic volume in 92 patients (61 treated and 31 placebo controls) with ischemic cardiomyopathy who underwent intramyocardial delivery of autologous bone marrow mononuclear cells (BMMC).8 However, a significant improvement (2.7%) in left ventricular ejection fraction (LVEF) was observed that was directly related to both cell composition (higher CD34+ or CD133 cell counts) and patient age, consistent with an observed age-related decline in the number and potency of autologous BMMCs.9,10 This has stimulated interest in alternative mechanisms to enhance the effectiveness of cell therapy, including the

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Ixmyelocel-T is an expanded multicellular therapy cultured from autologous BMMC comprised myeloid cells (ie, granulocytes, monocytes, and mixed myeloid progenitors) and lymphoid cell types (ie, T cells, B cells, and mixed lymphoid progenitors) that express CD45+ on the cell surface, as well as CD90+ mesenchymal stromal cells. Within the population of CD45+ cells is a subpopulation of CD45+CD14+ autologous (CD14+Auto+) M2-like macrophages. Although all of these cell types are found in bone marrow, the number and proportion of CD90+ and CD14+Auto+ cells are significantly greater in the ixmyelocel-T product as a result of expansion during the manufacturing process. In comparison with the relatively small reservoir of these 2 cell types in bone marrow, ixmyelocel-T contains 200- and 50-fold the number of M2-like macrophages and mesenchymal stromal cells, respectively.

A range of biological activities relevant to tissue repair and regeneration has been demonstrated reflecting the multicellular composition of ixmyelocel-T. In addition, ixmyelocel-T was associated with improved ischemic ulcer healing and a reduction in the rate of amputation in a placebo-controlled phase 2 study in patients with critical limb ischemia.

We report here the results of 2 phase 2A clinical trials of intramyocardial delivery of ixmyelocel-T in patients with end-stage HF because of ischemic and nonischemic dilated cardiomyopathy (DCM).

Methods

Study Design

Two prospective, randomized, open-label, multicenter, phase 2A trials were conducted to assess the safety and efficacy of ixmyelocel-T administered via minithoracotomy or intramyocardial catheter injection with the NOGA Myostar in patients with DCM stratified by ischemic or nonischemic status.

The surgical study (IMPACT-DCM; ClinicalTrials.gov Identifier: NCT00765518) was conducted from November 2008 to September 2012. Eligible patients were randomized to either ixmyelocel-T or standard of care control in a 3:1 ratio (n = 39). The catheter study (Catheter-DCM; NCT01020968) was conducted from April 2010 to March 2013. Eligible patients were randomized to either ixmyelocel-T or standard of care control in a 2:1 ratio (n = 22). The catheter study (Catheter-DCM; NCT01020968) was conducted from April 2010 to March 2013. Eligible patients were randomized to either ixmyelocel-T or standard of care control in a 2:1 ratio (n = 22).

In Catheter-DCM, each injection contained 0.2 mL of ixmyelocel-T suspension delivered via a 1-mL syringe into the midmyocardium at each of the injection sites. In IMPACT-DCM, patients received ixmyelocel-T injections via minimally invasive thoracotomy or lateral thoracotomy (determined by the treating cardiac surgeon) to 25 to 50 injection sites equally distributed (medially and laterally) across the anterior and posterior areas of the left ventricular wall. Injection sites were a minimum of 1 cm apart and designed to encompass as much of the ventricular-free wall as possible. Each injection contained 0.2 mL of ixmyelocel-T suspension delivered via a 1-mL syringe into the midmyocardium at each of the injection sites. In Catheter-DCM, ixmyelocel-T was delivered percutaneously via the NOGA XP catheter delivery system (Biologics Delivery Systems Group of Cordis Corporation, a Johnson & Johnson company, Irwindale, CA) with a series of 12 to 20 injections of 0.4 mL each 2 cm apart into the myocardium. For ischemic patients, ixmyelocel-T injections were performed within 2 cm of the border between viable and infarcted (<6 mV unipolar voltage) myocardium. For nonischemic patients, ixmyelocel-T injections were distributed equally among the anterior, lateral, and posterior left ventricular wall, avoiding the intraventricular septum and areas where wall thickness was <6 mm. All injections were made into viable myocardium with unipolar voltage ≥6.0 mV and loop stability ≤3 mm. The mean (±SD) volume of injections for Catheter-DCM was 13 ± 1.6 and for IMPACT-DCM 25 ± 2.6.

In the control group received standard-of-care treatment for DCM, according to accepted medical practices. After a data review by the Data Safety Monitoring Board, patients in the control group were randomized to either Catheter-DCM or IMPACT-DCM.
Definitions and End Points

The primary objective of the studies was to assess the safety of ixmyelocel-T. The secondary objectives were to assess the efficacy of ixmyelocel-T when compared with control (standard of care) within each DCM stratum (ischemic and nonischemic) and pooled across strata. Efficacy was evaluated at 1 (IMPACT-DCM only), 3, 6, and 12 months. Major adverse cardiac events (MACE) included cardiac death, cardiac arrest, myocardial infarction, sustained ventricular arrhythmia (eg, ventricular tachycardia or ventricular fibrillation), pulmonary edema, HF exacerbation requiring hospitalization (eg, acute HF), unstable angina, or major bleeding (defined as the need for ≥2 units of blood within 1 week of injection procedure or the need for operation because of bleeding). Changes from baseline in NYHA HF status, Minnesota Living with Heart Failure Questionnaire (MLHFQ), and in exercise tolerance measured by 6-minute walk test were evaluated, as well as C-reactive protein and brain natriuretic peptide. Structural assessments from echocardiogram and SPECT (single-photon emission computed tomography) were read by a blinded core laboratory and included changes from baseline in LVEF, LV dimensions and volumes, wall motion score index, and myocardial perfusion.

Data Analysis

Both studies were phase 2A and designed to evaluate safety and explore potential efficacy. Neither study was powered to test a prospective hypothesis. A computer-generated randomization schedule was used to assign patients within each stratum. Control patients underwent an initial follow-up visit ∼30 days after their screening visit, which was considered day 0 and baseline for data display and summary of adverse events. There was no imputation for missing data. Data from the randomized portion of the study were summarized using descriptive statistics. Differences between groups in the change from baseline were analyzed using a 2 sample unpaired t test. Differences between groups in baseline demographics were compared by an unpaired t test. The proportion of patients who were men, white, experienced a MACE, or achieved a NYHA class I/II was tested using a 2-tailed Fisher exact test. A P value of <0.05 was considered statistically significant. MACEs were adjudicated in a blinded fashion by the Principal Investigators (T.D.H. and A.N.P.). MACE was summarized by the number of patients who experienced a MACE overall and by the number of patients experiencing a specific event categorized as MACE. Treatment-emergent adverse events were summarized by the number of events per patient. For this analysis, a patient was counted only once, regardless of the number of MACE events experienced.

Results

Study Disposition

In the IMPACT-DCM study (n=39), 24 of 25 patients randomized to ixmyelocel-T treatment were treated and 14 patients were in the standard of care (control) group (Figure 1). One aspirate had an inadequate number of mononuclear cells for expansion. In the Catheter-DCM study (n=22), 15 patients were aspirated and received ixmyelocel-T and 7 patients were in the control group. After 6 months in the surgical study or 12 months in the catheter study, 8 control patients met eligibility criteria, underwent a successful bone marrow aspiration, and were subsequently treated with ixmyelocel-T. Between the 2 studies, a total of 61 patients were randomized. A total of 21 patients

![Figure 1. Patient disposition.](http://circres.ahajournals.org/)

Eligible patients with dilated cardiomyopathy (DCM), stratified by ischemic/nonischemic disease, were enrolled in 2 randomized open-label feasibility studies and followed up for ≤24 months. In the IMPACT-DCM study, ixmyelocel-T was administered via minithoracotomy. In the Catheter-DCM study, ixmyelocel-T was administered with a NOGA Myostar injection catheter. The numbers of patients randomized, treated, and followed up for 12 months after treatment is shown for each study by strata. Patients randomized to control (standard of care) were given the opportunity to be rescreened after 6 months in the IMPACT-DCM study or after 12 months in the Catheter-DCM study and, pending eligibility, receive ixmyelocel-T. Safety and a limited number of efficacy assessments were evaluated in the study extensions.
with ischemic DCM received ixmyelocel-T, whereas 9 patients with ischemic DCM served as controls. Eighteen patients with nonischemic DCM received ixmyelocel-T, whereas 11 patients with nonischemic DCM served as controls. A total of 59 patients were evaluated in the combined study results because 1 patient failed aspiration and 1 patient withdrew consent.

Baseline characteristics of the control and ixmyelocel-T–treated populations were similar in both studies (Table 1). In the combined ischemic and nonischemic populations from both studies, the majority of patients were men and white. All but 2 patients were NYHA class III. All ischemic patients were men, whereas nonischemic patients were more likely to be women and slightly younger. Patients with nonischemic cardiomyopathy were a heterogeneous group as expected but did not have coronary artery disease. The Catheter-DCM ischemic control group (n=3) had significantly lower LVEF (15.5%) than the ixmyelocel-T–treated group (n=9; 25.4%). Baseline left ventricular end-diastolic volume, end-systolic volume, 6-minute walk distance (6MWD), and MLHFQ global score values were similar across all other groups. Given the small number of control patients in each strata, data from the 2 studies were combined for end point evaluation.

### Safety

The mean number of adverse events per patient is shown for individual studies by treatment group and displayed by days 0 to 5 and day 6 to 730 (Table 2). Only ixmyelocel-T–treated patients underwent minithoracotomy, thoroscopy, or catheter procedure. The 5 most common adverse events that occurred in the ixmyelocel-T group (ischemic and nonischemic) during the surgical procedure (days 0–5) were hypotension, nausea, constipation, hyperglycemia, and hypertension. Surgical delivery of ixmyelocel-T was associated with a higher incidence of SAEs in the perisurgical period (days 0 to 5). A similar

<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristic</th>
<th>Ischemic</th>
<th>Nonischemic</th>
<th>Combined</th>
<th>P Value</th>
<th>Ischemic</th>
<th>Nonischemic</th>
<th>Combined</th>
<th>P Value</th>
<th>Ischemic</th>
<th>Nonischemic</th>
<th>Combined</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male sex, n (%)</td>
<td>9 (100)</td>
<td>21 (100)</td>
<td></td>
<td>1.00</td>
<td>7 (64)</td>
<td>13 (73)</td>
<td></td>
<td>0.69</td>
<td>16 (80)</td>
<td>34 (87)</td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>Age, y, mean (SD)</td>
<td>63.2 (12)</td>
<td>64.7 (9)</td>
<td></td>
<td>0.75</td>
<td>52.3 (11)</td>
<td>57.9 (11)</td>
<td></td>
<td>0.19</td>
<td>57.2 (13)</td>
<td>61.6 (11)</td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Combined Race, n (%)</td>
<td>67.0 (14)</td>
<td>66.4 (12)</td>
<td>0.94</td>
<td></td>
<td>46.7 (16)</td>
<td>60.3 (16)</td>
<td>0.27</td>
<td></td>
<td>56.8 (17)</td>
<td>64.0 (14)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NYHA class, n (%)</td>
<td>9 (100)</td>
<td>20 (95)</td>
<td>1.00</td>
<td></td>
<td>10 (91)</td>
<td>15 (83)</td>
<td>1.00</td>
<td></td>
<td>19 (95)</td>
<td>35 (90)</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combined LVEF, %, mean (SD)</td>
<td>25.4 (10)</td>
<td>27.2 (7)</td>
<td>0.58</td>
<td></td>
<td>24.7 (6)</td>
<td>25.8 (7)</td>
<td>0.67</td>
<td></td>
<td>25.0 (8)</td>
<td>26.5 (7)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combined LVEDV, mL, mean (SD)</td>
<td>237.3 (42)</td>
<td>204.6 (59)</td>
<td>0.20</td>
<td></td>
<td>223.5 (94)</td>
<td>215.7 (95)</td>
<td>0.83</td>
<td></td>
<td>229.2 (75)</td>
<td>209.9 (82)</td>
<td>0.38</td>
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<tr>
<td></td>
<td>Combined LVESV, mL, mean (SD)</td>
<td>178.3 (45)</td>
<td>151.6 (60)</td>
<td>0.24</td>
<td></td>
<td>169.0 (72)</td>
<td>163.4 (83)</td>
<td>0.85</td>
<td></td>
<td>172.8 (61)</td>
<td>157.3 (71)</td>
<td>0.41</td>
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<tr>
<td></td>
<td>Combined 6-Min walk distance, m, mean (SD)</td>
<td>166.3 (38)</td>
<td>149.2 (74)</td>
<td>0.61</td>
<td></td>
<td>167.5 (72)</td>
<td>171.9 (76)</td>
<td>0.90</td>
<td></td>
<td>167.0 (58)</td>
<td>161.1 (84)</td>
<td>0.82</td>
<td></td>
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<tr>
<td></td>
<td>Combined MLHFQ Global Score, mean (SD)</td>
<td>54.9 (28)</td>
<td>46.5 (23)</td>
<td>0.40</td>
<td></td>
<td>48.4 (22)</td>
<td>55.8 (21)</td>
<td>0.37</td>
<td></td>
<td>51.3 (24)</td>
<td>50.8 (22)</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combined Catheter</td>
<td>47.0 (28)</td>
<td>49.7 (24)</td>
<td>0.83</td>
<td></td>
<td>51.1 (21)</td>
<td>53.9 (21)</td>
<td>0.77</td>
<td></td>
<td>49.4 (23)</td>
<td>51.8 (22)</td>
<td>0.75</td>
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<tr>
<td></td>
<td>Combined Catheter</td>
<td>70.7 (24)</td>
<td>42.3 (23)</td>
<td>0.10</td>
<td></td>
<td>41.0 (26)</td>
<td>59.7 (21)</td>
<td>0.28</td>
<td></td>
<td>55.8 (28)</td>
<td>49.3 (23)</td>
<td>0.59</td>
<td></td>
</tr>
</tbody>
</table>

LVEDV indicates left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; and MLHFQ, Minnesota Living with Heart Failure Questionnaire.
was no change from baseline in stroke volume and cardiac output in any treatment group. No differences from baseline were observed in C-reactive protein (mean±SEM) at 3 months (4.7±0.9 versus 5.8±1.4 mg/L) or brain natriuretic peptide (mean±SEM) at 12 months (502±71 versus 451±63 ng/L) in the ixmyelocel-T–treated patients.

**Discussion**

The objective of these 2 studies was to evaluate the safety and feasibility of 2 methods of ixmyelocel-T cell delivery, as well as to identify potential clinical benefit. Despite a small number of patients treated in the individual studies, the combined data suggest that intramyocardial injection with ixmyelocel-T reduces MACE and improves symptoms in patients with ischemic DCM but not in patients with nonischemic DCM. Given the similar study design, including stratification by ischemic versus nonischemic cause, similar eligibility criteria, and patient follow-up, we elected to present both studies together. There were other slight differences between the studies, including the pattern of intramyocardial injection pattern.

On the basis of the increased incidence of adverse events associated with ixmyelocel-T administration via minimally invasive thoracoscopy or lateral thoracotomy compared with the catheter administration, we selected catheter administration for an ongoing phase 2 double-blind, placebo-controlled trial in patients with ischemic cardiomyopathy (ClinicalTrials.gov Identifier: NCT01670981). Notably, the number of SAEs in treated or standard of care patients in both studies did not differ during the 2-year follow-up period, starting on day 6. Numeric and clinically meaningful improvement in NYHA class, MLHFQ score, and 6MWD was observed in the ischemic patients starting 1 month after treatment and was sustained through 12 months. In addition, the number of MACE was lower in the treated ischemic patients when compared with that in the ischemic control patients, even when considering that 2 of the MACE (ventricular arrhythmia) in the treated patients seem to be related to the surgical procedure. The improvement in LV function from cell therapy overall has been moderate.5–7

Although the cell types are similar to those found in the BMMC population, the numbers of CD90+ and CD14+Auto+ cells are significantly greater in ixmyelocel-T. The prevailing scientific view is that a mixture of regenerative cell types, such as mesenchymal stromal cells and alternatively activated macrophages (CD90+ and CD14+Auto+, respectively), rather than a single cell type, are required to promote long-term tissue regeneration and repair22,23. On the basis of preclinical data, we found that ixmyelocel-T provides benefit via a

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**Table 2. Summary of Adverse Events Per Patient**

<table>
<thead>
<tr>
<th>Days 0–5</th>
<th>Days 6–730</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ixmyelocel-T</td>
<td>Control</td>
</tr>
<tr>
<td>Surgical study (IMPACT-DCM)</td>
<td>6.71</td>
</tr>
<tr>
<td>Catheter study (Catheter-DCM)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

DCM indicates dilated cardiomyopathy.

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**Table 3. Summary of MACE**

<table>
<thead>
<tr>
<th>IMPACT-DCM (6 mo)</th>
<th>Catheter-DCM (1 y)</th>
<th>Both Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Ixmyelocel-T</td>
</tr>
<tr>
<td>No./n (%) of patients with a MACE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>3/6 (50)</td>
<td>2/12 (17)</td>
</tr>
</tbody>
</table>

DCM indicates dilated cardiomyopathy; and MACE, major adverse cardiac event.

*indicates statistically significant (P<0.05) differences between groups.
multimodal mechanism of action, including a local paracrine effect given its cytokine expression profile.16 Either the CD90+ or CD14+Auto+ cells from ixmyelocel-T secrete 10-fold more anti-inflammatory cytokines interleukin 1-α, interleukin-10, macrophage inflammatory protein-1α and growth factors vascular endothelial growth factor and hepatocyte growth factor than BMMCs. In a rat model of chronic arterial occlusion, nonclassically activated anti-inflammatory macrophages (such as the CD14+Auto+ macrophages in ixmyelocel-T) have been demonstrated to play a role during collateral growth.24 M2 macrophages increased in number in the perivascular space after occlusion. Interleukin-10 treatment, known to induce M2 activation, led to perfusion recovery, indicating that the M2 macrophage is critical for collateral growth.

Limitations

The major limitation for both trials is the lack of true placebo groups. A recent meta-analysis of cell therapy treatment after an acute myocardial infarction suggests that the lack of placebo may overestimate the treatment effect.25 We noted differences in both the standard of care populations and treated patients based on the cause of DCM, with higher events in the ischemia patients. Assuming the placebo effect on secondary end points, such as NYHA class, 6MWD, and MLHFQ, would be the same in the 2 treated populations; these results

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Table 4. Listing of MACE by Strata and Treatment Group

<table>
<thead>
<tr>
<th>MACE No./N (%) of Patients*</th>
<th>Ischemic</th>
<th>Nonischemic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Ixmyelocel-T</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>1 (11)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Ventricular arrhythmia†</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>CHF exacerbation</td>
<td>4 (44)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure; and MACE, major adverse cardiac event.

*Patients may have had multiple events in different MACE categories; therefore, columns with specific events do not add up to the row value for any MACE shown in Table 3.

†Two cases of ventricular arrhythmia occurred during the surgical procedure.

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Figure 2. Efficacy assessments. Postbaseline efficacy assessments of patients from both studies are shown. The percentage of control patients (-) or ixmyelocel-T–treated patients (●) with a New York Heart Association (NYHA) class score of I or II is shown for (A) ischemic and (B) nonischemic patients. Change from baseline in Minnesota Living with Heart Failure Questionnaire (MLHFQ) global score (mean and SEM) for control patients (-) or for ixmyelocel-T–treated patients (●) is shown for (C) ischemic and (D) nonischemic patients. Change from baseline in 6-minute walk distance (6MWD, mean and SEM) for (E) ischemic and (F) nonischemic patients. An asterisk (*) indicates statistically significant (P<0.05) differences between groups.

Figure 3. Cardiac structure and function. Change from baseline in left ventricular ejection fraction (LVEF, %) is shown for control patients (-) or ixmyelocel-T–treated patients (●) for (A) ischemic and (B) nonischemic patients. Change from baseline in LV end-systolic volume is shown for control patients (-) or ixmyelocel-T–treated patients (●) for (C) ischemic and (D) nonischemic patients. Change from baseline in LV end-diastolic volume is shown for control patients (-) or for ixmyelocel-T–treated patients (●) for (E) ischemic and (F) nonischemic patients. There were no statistically significant differences (P<0.05) between groups.
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Disclosures
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References
11. Hare JM, Fishman JE, Gerstenblith G, et al. Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by...


Novelty and Significance

What Is Known?

• Results of clinical trials with bone marrow mononuclear cells demonstrate safety but only modest efficacy.

• The number and potency of stem cells decline with age and cardiac risk factors.

• Ixmyelocel-T is an expanded multicellular therapy cultured from autologous bone marrow mononuclear cells that contain ~200-fold the number of M2-like macrophages and mesenchymal stem cells than bone marrow mononuclear cells, respectively.

What New Information Does This Article Contribute?

• In 2 randomized, open-label studies, intramyocardial injection with ixmyelocel-T was associated with a reduction in the number of patients with major adverse cardiovascular events and improved symptoms in patients with ischemic dilated cardiomyopathy (DCM) but not in patients with nonischemic DCM.

• There were fewer adverse events associated with ixmyelocel-T administration via catheter in comparison with minimally invasive thoracoscopy or lateral thoracotomy.

• These results strengthen the rationale for the design of the ongoing phase 2B randomized double-blind, placebo-controlled ixCELL-DCM trial.


Safety and Efficacy of Ixmyelocel-T: An Expanded, Autologous Multi-Cellular Therapy, in Dilated Cardiomyopathy

Timothy D. Henry, Jay H. Traverse, Baron L. Hammon, Cara A. East, Brian Bruckner, Ann E. Remmers, David Recker, David A. Bull and Amit N. Patel

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**Supplemental Table**

Summary of Deaths, LVAD placements, and Heart Transplants

<table>
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<th>IMPACT-DCM (6 months)</th>
<th>Catheter-DCM (1 year)</th>
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<td>Ixmyelocel-T</td>
<td>Control</td>
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<td><strong>Number/N (%) of Deaths</strong></td>
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<td>Ischemic</td>
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<td><strong>Number/N (%) of Heart Transplants</strong></td>
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<td><strong>Number/N (%) of LVAD placements</strong></td>
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<tr>
<td>Nonischemic</td>
<td>1/8 (15)</td>
<td>3/12 (25)</td>
<td>1/3 (33)</td>
</tr>
</tbody>
</table>

**Supplemental Methods**

**Impact-DCM surgical study eligibility criteria**

**Inclusion Criteria**

1. Diagnosis of ischemic or nonischemic dilated cardiomyopathy according to WHO criteria:
   - Dilatation and impaired contraction of the left ventricle or both ventricles of idiopathic, familial/genetic, viral and/or immune, toxic origin, or associated with recognized cardiovascular disease in which the degree of myocardial dysfunction is not explained by the abnormal loading conditions or the extent of ischemic damage (Richardson P; et al., 1996)
   
   **Or**
   - Ischemic dilated cardiomyopathy is defined as dilated cardiomyopathy in a patient with a history of myocardial infarction or evidence of clinically significant (≥70% narrowing of a major epicardial artery) coronary artery disease (Bristow MR; et al., 1991).

2. No other cardiac surgery or percutaneous cardiac interventions are likely to produce clinical improvement, in the opinion of the investigator (cardiac surgeon) and the referring interventional cardiologist.

3. Left ventricular ejection fraction ≤30% by echocardiogram.

4. Symptomatic heart failure in NYHA functional class III or IV defined by:
NYHA class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.

NYHA class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. Note: Only those patients who can tolerate surgery and are not actively receiving inotropes should be included.

5. Able to comply with scheduled visits in cardiac out-patient clinic.
6. Able to tolerate study procedures, including bone marrow aspiration, left lateral thoracotomy or thoracoscopy with single lung ventilation, MRI or cardiac CT, spirometry and 6 minute walk test.
7. Males and females, 18-86 years of age.
8. Life expectancy of 6 months or more in the opinion of the investigator.
9. Able to give informed consent.
10. Normal organ and marrow function as defined:
    - Leukocytes $\geq 3,000/\mu L$
    - Absolute neutrophil count $\geq 1,500/\mu L$
    - Platelets $\geq 140,000/\mu L$
    - AST (SGOT)/ALT (SGPT) $\leq 2.5 \times$ institutional standards range
    - Creatinine $\leq 2.5$ mg/dL
11. Adequate pulmonary function defined by forced expiratory volume in one second (FEV1) >50% of predicted.
12. Controlled blood pressure (defined as a systolic blood pressure $\leq 140$ and a diastolic blood pressure of $\leq 90$ mmHg) and established anti-hypertensive therapy as necessary prior to entry into the study.
13. Adequate medical management of DCM and other pre-existing conditions (e.g., hypercholesterolemia, thromboembolic risk).

The adequate medical management of DCM includes the following:
- Placement of an automated implantable cardioversion defibrillator (AICD) unless contraindicated (e.g., due to patient profession). Patient refusal of AICD placement is not considered a valid contraindication.
- Use of ACE inhibitors and/or AT-1 receptor blockers as well as loop diuretics (e.g., furosemide).
- Depending on the type of heart failure associated with the disease, therapy may also include the use of vasodilators (e.g., nitrates or hydralazine), beta blockers (e.g. long-acting metprolol or carvedilol), digoxin, and aldosterone antagonists (e.g. spironolactone or canrenoate).
A drug treatment regimen for their DCM must have been established for at least one month with no new medications to treat the disease introduced in the last 3 months.

Fertile patients must agree to use an appropriate form of contraception while participating in the study.

Exclusion Criteria

1. Severe primary valvular heart disease including, but not limited to, aortic valve stenosis and insufficiency.

2. Known history of Chronic Obstructive Pulmonary Disease (COPD) defined as Gold stages IIB (FEV1/FVC<70% with FEV1<50% predicted, with or without chronic symptoms of cough, sputum production, dyspnea) or more severe or restrictive pulmonary disease.

3. Known history of primary pulmonary hypertension.

4. Ventricular Assist Device (VAD) implantation.

5. Myocardial infarction within 4 weeks prior to randomization.

6. Life-threatening ventricular arrhythmia, except if an implantable cardioverter defibrillator (ICD) is implanted.

7. Unstable angina, characterized by increasingly frequent episodes with modest exertion or at rest, worsening severity, and prolonged duration.

8. Patients receiving treatment with hematopoietic growth factors (e.g. EPO, GM-CSF).

9. Patients who require uninterruptible anticoagulation or anti-platelet therapy [i.e. anticoagulation therapy (e.g. warfarin) that cannot be stopped for 72 hours prior to bone marrow aspiration and intramyocardial injections].

10. Known cancer and undergoing treatment including chemotherapy and radiotherapy.

11. Patients who will require continuous, systemic, high dose corticosteroid therapy (more than 7.5 mg/day) within 6 months after surgery.

12. End stage renal disease requiring dialysis.

13. Patients who are pregnant or lactating; positive for hCG.

14. History of alcohol consumption regularly exceeding the equivalent of 2 drinks/day (1 drink = 5 oz of wine or 12 oz [360mL] of beer or 1.5 oz [45mL]) of hard liquor or history of illicit drug use within 6 months of screening.

15. Known allergies to protein products (horse or bovine serum, or porcine trypsin) used in the ex-vivo cell production process.

16. Body Mass Index (BMI) of 40 Kg/m² or greater.
17. Patients receiving experimental medications or participating in another clinical study within 30 days of screening.

18. HIV or syphilis, positive at time of screening.

19. Active Hepatitis B, or Hepatitis C infection at the time of screening.

20. In the opinion of the investigator, the patient is unsuitable for cellular therapy.

21. Patients receiving anti-angiogenic drugs (e.g. anti-VEGF).

Catheter-DCM study eligibility criteria

Inclusion Criteria

1. Diagnosis of ischemic or non-ischemic dilated cardiomyopathy according to WHO criteria:
   - Ischemic dilated cardiomyopathy is defined as dilated cardiomyopathy in a patient with a history of myocardial infarction or evidence of clinically significant (≥70% narrowing of a major epicardial artery) coronary artery disease (Bristow MR; et al., 1991).
   - Non-ischemic dilated cardiomyopathy is defined as dilatation and impaired contraction of the left ventricle or both ventricles of idiopathic, familial/genetic, viral and/or immune, toxic origin, or associated with recognized cardiovascular disease in which the degree of myocardial dysfunction is not explained by the abnormal loading conditions or the extent of ischemic damage (Richardson P; et al., 1996).

2. No other cardiac surgery or percutaneous cardiac interventions are likely to produce clinical improvement and confirmed by an interventional cardiologist (for PTCA) and a cardiothoracic surgeon (for CABG). This condition is satisfied in patients with chronic ischemic disease when a patient has previously been successfully revascularized but has failed to show clinical improvement. All patients who are candidates for revascularization are considered not eligible for participation in the study. (For patients diagnosed with non-ischemic disease, there is no need for a cardiothoracic surgeon consult.)

3. Left ventricular ejection fraction ≤30% by echocardiogram, per assessment performed within 30 days prior to randomization.

4. Symptomatic heart failure in NYHA functional class III or IV defined by:
   - NYHA class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
   - NYHA class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

5. Able to comply with scheduled visits in cardiac out-patient clinic.
6. Able to tolerate study procedures, including bone marrow aspiration, metabolic stress test, 6 minute walk test. Patients must also be able to tolerate NOGA mapping.

7. Males and females, 18-86 years of age.

8. Life expectancy of 6 months or more in the opinion of the investigator.

9. Able to give informed consent.

10. Normal organ and marrow function as defined:
    - Leukocytes ≥3,000/μL
    - Absolute neutrophil count ≥1,500/μL
    - Platelets ≥140,000/μL
    - AST (SGOT)/ALT (SGPT) ≤2.5 X institutional standards range
    - Creatinine ≤ 2.5 mg/dL

11. Controlled blood pressure (defined as a systolic blood pressure ≤140 and a diastolic blood pressure of ≤90 mmHg) and established anti-hypertensive therapy as necessary prior to entry into the study.

12. Patient has received stable, standard medical therapy for DCM for at least one month with no new medications to treat the disease introduced in the last 3 months. Standard medical therapy includes the following:
    - Placement of an automated implantable cardioverter defibrillator (AICD) unless contraindicated (e.g., due to patient profession, etc.). Patient refusal of AICD placement is not considered a valid contraindication. If a bi-ventricular pacer/ICD has been placed, the patient must wait 3 months from time of placement before randomization.
    - Use of ACE inhibitors and/or AT-1 receptor blockers unless contraindicated, and use of loop diuretics (e.g., furosemide) as dictated by a patient’s current medical condition.
    - Depending on the type of heart failure associated with the disease, standard therapy may also include the use of vasodilators (e.g., nitrates or hydralazine), beta blockers (e.g. long-acting metprolol or carvedilol), digoxin, and aldosterone antagonists (e.g. spironolactone or canrenoate), or other medications.

13. Pre-existing conditions (e.g., hypercholesterolemia, thromboembolic risk, diabetes) are adequately controlled in the opinion of the investigator.

14. Fertile patients (male and female) must agree to use an appropriate form of contraception while participating in the study.

**Exclusion Criteria**

1. Severe primary valvular heart disease including, but not limited to, aortic valve stenosis and insufficiency. Patients with aortic valve prosthesis, artificial or animal derived, are also excluded.
2. Known history of Chronic Obstructive Pulmonary Disease (COPD) defined as Gold stage IIB (FEV1/FVC<70% with FEV1 30% - 49% of predicted, with or without chronic symptoms of cough, sputum production, dyspnea) or more severe or restrictive pulmonary disease.

3. Known history of primary pulmonary hypertension.

4. Ventricular Assist Device (VAD) implantation.

5. Myocardial infarction within 4 weeks prior to randomization.

6. History of life-threatening ventricular arrhythmia, except if an automated implantable cardioverter defibrillator (AICD) is implanted.

7. Unstable angina, characterized by increasingly frequent episodes with modest exertion or at rest, worsening severity, and prolonged duration.

8. Patients who are at high risk for complications due to the injection procedure (e.g., patients who have severe peripheral atherosclerotic disease that does not allow advancement of the catheter; patients who have a prosthetic aortic or mitral valve; patients who have a left ventricular thrombus or aneurysm; patients who have an aortic dissection or aneurysm, etc.).

9. Patients with poorly controlled diabetes mellitus (HbA1c > 9.0%).

10. Patients receiving treatment with hematopoietic growth factors (e.g., EPO, G-CSF).

11. Patients who are unable to tolerate institutional guidelines regarding anticoagulant and anti-platelet therapy during bone marrow aspiration and transendocardial injections.

12. Known cancer and undergoing treatment including chemotherapy and radiotherapy.

13. Patients who will require continuous, systemic, high dose corticosteroid therapy (more than 7.5 mg/day) within 1 month before aspiration or 6 months after injection procedure.

14. End stage renal disease requiring dialysis.

15. Patients who are pregnant or lactating; positive for hCG

16. History of alcohol consumption regularly exceeding the equivalent of 2 drinks/day (1 drink = 5 oz of wine or 12 oz [360mL] of beer or 1.5 oz [45mL]) of hard liquor or history of illicit drug use within 6 months of screening.

17. Known allergies to protein products (horse or bovine serum, or porcine trypsin) used in the ex-vivo cell production process.

18. Body Mass Index (BMI) of 40 Kg/m² or greater.

19. Patients receiving experimental medications or participating in another clinical study within 30 days of screening.

20. HIV or syphilis, positive at time of screening.

21. Active Hepatitis B or Hepatitis C infection at the time of screening.
22. In the opinion of the investigator or the sponsor, the patient is unsuitable for cellular therapy.

23. Patients receiving anti-angiogenic drugs (e.g. anti-VEGF).

24. In the opinion of the investigator, the patient’s LV wall thickness is unsuitable for cell injections.

**Supplemental References**
