12-13-2019

Effects of Stem Cell Therapy on 6-Minute Walk Test Distance and Left Ventricular Ejection Fraction in Patients with Nonischemic Cardiomyopathy

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Alexa Maziuk

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Effects of Stem Cell Therapy on 6-Minute Walk Test Distance and Left Ventricular Ejection Fraction in Patients with Nonischemic Cardiomyopathy

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James Madison University
ABSTRACT

Objective
To assess the efficacy of stem cells in the improvement of functional capacity and quality of life in the setting of nonischemic dilated cardiomyopathy.

Design
Systematic literature review

Methods
A literature search of PubMed was conducted utilizing the following search terms: “stem,” “cell,” “nonischemic,” and “cardiomyopathy.” The following limits were used: “2015-2018,” nonischemic cardiomyopathy, results of LVEF and 6MWT, randomized controlled trials, pilot studies, and sample size >22.

Results
Butler et al. found that within the itMSC group, 6MWD increased by an average of 27.40 m (95% CI 0.28–54.52; P=0.05), but it decreased by an average of 10.83 m (95% CI −38.66 to 17.00, P=0.45) among control patients. The authors used exploratory analyses to examine changes from baseline after initial randomization and found significant increases in LVEF in the itMSC group (estimated mean difference was +2.31; P=0.02) with no significant changes in control group (+1.62; P=0.13). Vrtovec et al. revealed improvement in LVEF and 6MWT in both single and repetitive dose groups (group A and group B), when comparing each group separately from baseline to 6 months (LVEF: +6.9±3.3% in group A, P=0.001 and +7.1±3.5% in group B, P=0.001; 6MWT: +87±21 m, P=0.03 and +92±25 m, P=0.02). Hare et al. found that at 12 months post-treatment, LVEF increased in the allo-hMSC group by 8.0% (CI: 2.8% to 13.2%, p = 0.004) compared to baseline which was found to be statistically significant, but the LVEF increase of 5.4% in the auto-hMSC group was not statistically significant (CI: -1.4% to 12.1%; p = 0.116). At 12 months post-treatment, the 6MWT distance significantly increased in the allo-hMSC treatment group by 37.0 meters (CI: 2.0m to 72.0m, p = 0.04) compared to baseline. At 12 months post-treatment, the auto-hMSC treatment group 6MWT distance increased 7.3 meters compared to baseline and was not statistically significant (CI: -47.8m to 33.3m, p = 0.71).
Conclusion
Stem cell therapy is shown to be safe, well-tolerated, and effective in improving functional capacity, quality of life, and short-term event survival in patients with nonischemic cardiomyopathy and, thus, is a promising alternative therapeutic option for patients with nonischemic cardiomyopathy and should be further explored in future studies.

Abbreviations and Acronyms
AMI - Acute myocardial infarction
CHF - Chronic heart failure
G-CSF - Granulocyte colony-stimulating factor
HFrEF - Heart failure with reduced ejection fraction
hMSC - Human mesenchymal stem cells
ICD - Implantable cardioverter defibrillator
LVEF - Left ventricular ejection fraction
LVAD - Left ventricular assist device
MSC - Mesenchymal stem cells
NIDCM - Nonischemic dilated cardiomyopathy
NYHA - New York Heart Association
PAD - Peripheral artery disease
6MWD - 6-minute walk distance
6MWT - 6-minute walk test
TE-SAE - Treatment-emergent serious adverse events
TESI - Transendocardial stem cell injection
VO2 - Peak oxygen uptake
INTRODUCTION

Nonischemic dilated cardiomyopathy (NIDCM), often referred to as heart failure with reduced ejection fraction (HFrEF), is a disorder characterized by progressive degeneration and structural change of cardiac tissue leading to impaired contractile function of the heart. Since the only curative therapy for NIDCM at this time is heart transplantation, the primary goals of treatment are to improve cardiac function, reduce the symptoms of heart failure, and delay the need for heart transplantation for as long as possible.\(^1\) The burden of this disease is significant as NIDCM is currently the most common cause of heart failure leading to heart transplantation, accounting for 49.8% of all heart transplantations performed between January 2009 and June 2016.\(^2\) Over the past decade, the number of donor hearts available per year has remained relatively stable, but the number of patients in advanced heart failure in need of transplantation has risen significantly.\(^3\) It is currently estimated that dilated cardiomyopathy is responsible for 10,000 deaths and 46,000 hospitalizations each year in the USA.\(^4\) There are up to 50,000 candidates for heart transplantation each year worldwide, but only 5,000 cardiac transplants are performed.\(^5\) Of those 10% who are lucky enough to receive a curative transplantation, 85% are expected to survive the first year post-transplant and mean survival time for all heart transplant recipients is estimated to be 11 years.\(^6\) The limited supply of donor hearts and the high pre- and post-heart transplant mortality rates is evidence of a great need for additional heart failure therapeutic and curative options.

Stem cell-based therapies seem to be a promising new treatment option for NIDCM based on the results of several early phase clinical trials. Stem cells are a population of immature, undifferentiated cells, which have the potential to develop into a number of different specialized cell types. In the setting of NIDCM, it is hypothesized that stem cells have the potential to 1) aid in cardiac myocyte regeneration, 2) secrete factors that reduce the rate of apoptosis of endogenous cardiac myocytes, 3) promote angiogenesis, 4) activate endogenous cardiac stem cells to promote regeneration of new healthy tissue, and 5) induce the release of large amounts of anti-inflammatory factors which possibly have a significant role in myocyte repair.\(^7\) The goal of stem cell therapy in the treatment of NIDCM is to regain normal function of a damaged heart without the need for total heart transplantation.

End point measurements of cardiac improvement after stem cell therapy evaluated in this paper include the 6-minute walk test distance (6MWT) and left ventricular ejection fraction (LVEF). The 6MWT and LVEF are indicators of functional capacity in patients with heart failure. This review will focus on recent evidence that stem cell therapy causes short term improvement in the functional capacity of patients with nonischemic dilated cardiomyopathy.
METHODS

An initial literature search of PubMed was conducted in September 2018 using the following search terms: “stem,” “cell,” “nonischemic,” and “cardiomyopathy.” The initial search yielded 83 results, 47 of which were excluded when the results were filtered by year: “2015-2018.” The remaining 36 full-text articles were assessed for eligibility. Review articles, case reports, and animal trials were excluded. In addition, articles focusing on other disorders, without 6MWT as an outcome, and with sample size <22 were excluded. The three articles that remained were individually assessed using critical appraisal sheets and included in this analysis. A level of evidence was assigned to each study based on John Hopkins NURSING Evidence Level and Quality Guide. A summary of study criteria is shown in Table 1. The PRISMA flow chart, seen below in Figure 1, summarizes the article selection process.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
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<tbody>
<tr>
<td>Nonischemic Cardiomyopathy</td>
<td>Other diagnoses</td>
</tr>
<tr>
<td>Published within 2015-2018</td>
<td>Articles older than 3 years</td>
</tr>
<tr>
<td>Studies reporting LVEF and 6MWT</td>
<td>Studies not reporting 6MWT</td>
</tr>
<tr>
<td>Randomized controlled trials and pilot studies</td>
<td>Review articles, case reports, animal trials</td>
</tr>
<tr>
<td>Sample size &gt;22</td>
<td>Sample size &lt;22</td>
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</tbody>
</table>
**RESULTS**

**Study #1**

*Intravenous Allogeneic Mesenchymal Stem Cells for Nonischemic Cardiomyopathy. Safety and Efficacy Results of a Phase II-A Randomized Trial. Butler et al.*

**Study Objective**

“To assess the safety and preliminary efficacy of intravenously administered ischemia-tolerant MSCs (itMSCs) in patients with nonischemic cardiomyopathy.”
Study Design

This was a crossover randomized phase II-a trial involving 22 patients with nonischemic cardiomyopathy with LVEF less than or equal to 40%, from across 4 sites in the United States, between June 2014 and April 2016. Table 2 outlines patient inclusion and exclusion criteria. Thirty-four patients were screened, 23 were randomized, and 22 were involved in the study. Eligible patients were blinded to treatment allocation and randomized 1:1 to either the control group, “placebo-itMSC,” (n=12) or the intervention group, “itMSC” (n=10). Of note, the control group data was defined as the data from the group which received the placebo treatment at time t=0 days, "placebo-itMSC." The intervention group data was defined as the data from the group which received the intervention treatment at time t=0 days, "itMSC," as well as the data from "placebo-itMSC" from t=90 days to t=180 days. Both groups were evaluated from baseline at t=0 days through t=90 days before crossover. At t=90 days, the "placebo-itMSC" group received interventional treatment and the "itMSC" group received placebo treatment. The “itMSC” group received placebo after the crossover from t=90 days through t=180 days, but was not included in the data analysis of the control group. The intervention treatment was an intravenous (IV) infusion of ischemia-tolerant allogenic mesenchymal stem cells (MSCs) dosed at 1.5 million cells/kg extracted from the bone marrow of a healthy volunteer and suspended in Lactated Ringer’s solution at a concentration of 1x10^6 cells/mL. The placebo was an IV infusion of Lactated Ringer’s solution at 1 mL/kg. At t=90 days post-initial treatment, each group crossed over; the “placebo-itMSC” group received intervention and the “itMSC” group received placebo, resulting in each patient receiving a total of 2 infusions during the study. The study timeline and flow of patients through the trial can be seen in Figure 2. 

<table>
<thead>
<tr>
<th>Table 2: Study #1 Patient Criteria</th>
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</thead>
<tbody>
<tr>
<td><strong>Patient Inclusion Criteria</strong></td>
</tr>
<tr>
<td>Ambulatory</td>
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<tr>
<td>Chronic nonischemic cardiomyopathy</td>
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<tr>
<td>Baseline LVEF less than or equal to 40%</td>
</tr>
<tr>
<td>Older or equal to 18 years old</td>
</tr>
<tr>
<td>New York Heart Association (NYHA) Class III/IV symptoms</td>
</tr>
<tr>
<td>Receiving stable maximally tolerated medical therapy for greater than 6 months prior to randomization</td>
</tr>
</tbody>
</table>

CMR = Cardiac Magnetic Resonance
*Renal disease defined as: estimated GFR<30mL/min
**Liver disease defined as: AST/ALT > 3x normal, alkaline phosphatase or bilirubin > 2x normal
Prior to treatment, demographic data, New York Heart Association (NYHA) class, vital signs, laboratory data (AST/ALT, BNP, Troponin, Sodium, Creatinine, Total Bilirubin, and Albumin), medical history, medications, and cardiac magnetic resonance imaging were collected as baseline data. Mean age of study participants was 47.3 years, over two-thirds were Caucasian, all but one patient had NYHA class II symptoms, and rate of comorbidities was low. Secondary efficacy endpoints included LVEF and 6MWT, among others. LVEF was measured at baseline, t=90 days, and t=180 days and 6MWT was measured at t=30 days and t=90 days after initial and second transfusion. The flow of treatment can be seen in Figure 2 above. At each time point, vital signs, 12-lead electrocardiograms, and laboratory tests were collected. Twenty-four-hour Holter monitoring was also done at each time point up to t=270 days.

Figure 2: Study timeline and flow of patients through the trial

“CMR indicates cardiac magnetic resonance imaging; eGFR, estimated glomerular filtration rate; iMSc, ischemia-tolerant mesenchymal stem cells. A: Patient was hospitalized for worsening heart failure between time of screening and randomization.”
Statistical analyses used a 2-sided 0.05 significance level. Continuous secondary efficacy endpoints were analyzed using linear regression and 95% confidence intervals.

**Study Results**

At baseline, average LVEF was 31.6% ± 9.8%. At t=90 days, there was no significant difference between “placebo-itMSC” or “itMSC” groups as the estimated difference in LVEF was 0.01% (95% CI -1.50-1.52; P=0.99). However, increases in LVEF in the itMSC group were shown “in ad hoc exploratory analyses that examined changes from baseline after initial randomization (ie, first 90 days, pre crossover).” The estimated mean difference was +2.31 (P=0.02). During this same time period, changes in those patients who were receiving placebo were not significant with a LVEF estimated mean difference of +1.62 (P=0.13).

“Treatment with itMSCs resulted in statistically significant improvements in health status and functional capacity end points.” Compared to control, the change in six-minute walk distance (6MWD) from baseline to t=90 days after itMSC therapy was “significantly greater by 36.47 m (95% CI 5.98–66.97; P=0.02) or 15.9% [(See Figure 3)]. Specifically, within the “itMSC” group, 6MWD increased by an average of 27.40 m (95% CI 0.28–54.52; P=0.05), but it decreased by an average of 10.83 m (95% CI -38.66 to 17.00, P=0.45) among control patients.”

In summary, these results support clinical efficacy of IV stem cell infusion of ischemia-tolerant allogeneic MSCs in the setting of nonischemic dilated cardiomyopathy since a statistically significant improvement from baseline was seen in the “itMSC” group in 6MWD and in ad hoc exploratory analyses of LVEF, indicating a significant improvement of health status and functional capacity in these patients as a result of this experimental therapy. If results of this clinical trial are replicated in a larger randomized control trial, IV infusion of MSCs could be
considered as a less invasive therapeutic option to improve functional capacity as well as short-term event-free survival in patients with NIDCM.

**Study Critique**

Strengths of this study include the stringent inclusion and exclusion criteria as well as the rigorous definition of nonischemic cardiomyopathy defined using multiple clinical and objective parameters. Additionally, the use of multiple secondary efficacy endpoints helps to decrease the likelihood of chance findings when the results correspond. This study was also performed at 4 different sites in the US, limiting the chance of geographical elements.

This study is hampered by a small study size, though early phase studies primarily focusing on safety often have small sample sizes. The use of exploratory ad hoc analyses also provides an interesting challenge as significant results can be found, but still need prospective validation. The fact that this study was a crossover study can be both a strength and a hindrance. Crossover studies are helpful in that each participant acts as their own control, limiting between-subject variability. However, crossover studies are also a weakness as the researchers of this study “cannot definitively determine if any adverse event occurring>90 days after itMSC infusion within the itMSC–placebo group represents placebo effect, delayed consequence of cell therapy, or random chance.” An additional potential weakness in this study is that only MSCs grown under hypoxic conditions were used, due to previous studies reporting higher efficacy. The researchers did not test MSCs grown under normoxic conditions and, therefore, cannot conclude whether the ischemia-tolerant MSCs played a different role than that of normoxic MSCs.

Level of Evidence: 1B

**Study #2**

*Effects of Repetitive Transendocardial CD34+ Cell Transplantation in Patients With Nonischemic Dilated Cardiomyopathy. Vrtovec et al.*

**Study Objective**

To investigate if repetitive administration of CD34+ cells is more effective than single administration in patients with nonischemic dilated cardiomyopathy.
Study Design

This was a prospective randomized study involving 60 patients with nonischemic cardiomyopathy with LVEF less than or equal to 40%, “conducted at the Advanced Heart Failure and Transplantation Center at University Medical Center Ljubljana between January 2014 and September 2017 in collaboration with the Stanford Cardiovascular Institute.” Table 3 outlines patient inclusion and exclusion criteria. Of the 89 patients screened, 66 patients were enrolled, and 6 were excluded due to inadequate response to granulocyte colony-stimulating factor (G-CSF) stimulation, as the patient’s own stem cells were used for the transplantation. The remaining 60 patients were randomly allocated in 1:1 ratio to receive either repetitive (group A) or single-dose (group B) CD34+ cell therapy. “During 1-year follow-up, there was 1 heart transplantation in group A versus 1 death and 1 heart transplantation in group B. Of the 6 excluded patients, 1 patient died, and 1 underwent heart transplantation.” The study timeline and flow of patients through the trial can be seen in Figure 4.

<table>
<thead>
<tr>
<th>Patient Inclusion Criteria</th>
<th>Patient Exclusion Criteria</th>
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<tbody>
<tr>
<td>• Age 18 to 70 years</td>
<td>• Patients with acute multiorgan failure</td>
</tr>
<tr>
<td>• Diagnosis of DCM according to European Society of cardiology position statement</td>
<td>• History of hematologic neoplasms</td>
</tr>
<tr>
<td>• Optimal medical management for ≥3 months</td>
<td>• Inadequate response to G-CSF stimulation resulting in &lt;80 million CD34+ cells</td>
</tr>
<tr>
<td>• Left ventricular ejection fraction (LVEF) &lt;40%</td>
<td>• New York Heart Association functional class III for ≥3 months before referral</td>
</tr>
</tbody>
</table>
At baseline, demographic parameters, LVEF, exercise capacity, medications, comorbidities, and renal and liver function tests did not differ between groups. Mean age was 55±10. Both groups received daily subcutaneous injections of G-CSF (10 μg/kg) for 5 days. CD34+ cells were collected via apheresis with Miltenyi cell separator and the magnetic cell separator Isolex 300i was used for the immunomagnetic positive selection of the CD34+ cells. A standardized dose of 80 million CD34+ cells was used for transendocardial injection, guided by electronic mapping. In group A, G-CSF stimulation, apheresis, and cell injections were repeated at 6 months. Patients were followed for 1 year from baseline.

Figure 4: Flow chart of the study design

"Patients were randomly allocated in 1:1 ratio to receive either repetitive (group A) or single-dose (group B) cell therapy. At baseline, patients in both groups received G-CSF (granulocyte colony-stimulating factor); thereafter, CD34+ cells were collected via apheresis and injected transendocardially. In group A, G-CSF stimulation, apheresis, and cell injections were repeated at 6 months. Patients were followed for 1 year from baseline."
was a secondary end point, among others. “Favorable clinical response to cell therapy was defined as the presence of increase in LVEF of at least 5% at 6 months after stem cell transplantation.”

A blinded third party echocardiographer was recruited to analyze echocardiography data at the conclusion of the study and all of the data was averaged over 5 cycles. LVEF was estimated using the Simpson biplane method. In all patients, 6MWT was performed by a blinded observer. Patients who died or underwent heart transplantation were excluded from statistical analyses.

**Study Results**

At 1 year, there was no significant change in LVEF from 32.2±9.3% to 41.2±6.5% in group A and from 30.0±7.0% to 37.9±5.3% in group B, resulting in \( P=0.40 \). Additionally, there was no significant change in 6MWT between both groups at 1 year (from 320±92 to 434±71 m in group A and from 341±87 to 445±96 m in group B, \( P=0.65 \)). However, both groups showed improvement in LVEF and 6MWT, when comparing each group separately, from baseline to 6 months (LVEF: +6.9±3.3% in group A, \( P=0.001 \) and +7.1±3.5% in group B, \( P=0.001 \); 6MWT: +87±21 m, \( P=0.03 \) and +92±25 m, \( P=0.02 \)). In contrast, there were no significant changes between 6 months and 1 year in LVEF or 6MWT (LVEF: +2.1±2.3% in group A, \( P=0.19 \) and +0.8±3.1% in group B, \( P=0.5 \); 6MWT: +27±11 m, \( P=0.2 \) and +12±18 m, \( P=0.42 \)). These results are summarized below in Figure 5.

In summary, these results do not support clinical superiority of repetitive transendocardial CD34+ cell transplantation over single dose transplantation at this time. These results do show statistically significant improvement in both LVEF and the 6MWT in each separate group from baseline to 6 months; however, there was no significant improvement in LVEF or the 6MWT from 6 months to 1 year, suggesting a ceiling effect for cell therapy. If results of this clinical trial are replicated in a larger randomized control trial, transendocardial transplantation of CD34+ cells could be considered as an alternative.
therapeutic option to improve functional capacity as well as short-term event-free survival in patients with NIDCM.

**Study Critique**

Strengths of this study include the specific inclusion and exclusion criteria, with one of the inclusion criteria being NYHA class III symptoms. This is a strength because all individuals had comparable symptoms which ensured adequate and fair comparisons. These criteria also helped to create well-matched patient groups. In addition, included patients were followed in the researchers’ heart failure outpatient clinic for at least 3 months, which allowed for adequate optimization of medical therapy.

This study is hampered by the heterogeneity within the definition of DCM. Multiple tests were performed on each patient prior to inclusion, but no biopsies were done to exclude secondary cardiomyopathies. There was also no placebo arm which limits the evaluation of the cell therapy effects. This study was also performed only at one center, with a small sample size, and outside of the United States, which potentially limits the ability to extrapolate data to larger or geographically different populations. The echocardiography data was analyzed by one echocardiographer, which could be interpreted as a strength or a weakness. Although it provides a sort of uniformity, multiple interpreters at multiple centers could provide valuable information if there was interobserver agreement.

Level of Evidence: 1B

**Study #3**

*Randomized Comparison of Allogeneic Versus Autologous Mesenchymal Stem Cells for Nonischemic Dilated Cardiomyopathy. Hare et al.* 12

**Study Objective**

To evaluate the safety and efficacy of autologous versus allogeneic bone marrow-derived human mesenchymal stem cells (hMSCs) in Nonischemic Dilated Cardiomyopathy (NIDCM).
Study Design

This was a randomized control trial in which 37 patients were recruited from the University of Miami Hospital between December 2011 and July 2015 and randomized 1:1 to receive either allo- or auto-hMSCs by transendocardial stem cell injection (TESI) in 10 left ventricular sites. End points evaluated included LVEF and 6MWT, among others. Table 4 outlines inclusion criteria for this study.

Mean age of study participants was 55.8 years. 29% of participants were female, 35% were Hispanic, and 50% had NYHA functional class II symptoms. Average baseline test results for LVEF and 6MWT were 26.5% ± 9.64% and 422m ± 86.8m respectively.

Of the 37 patients who were randomized into one of the two groups of this study, 3 did not receive the study injection of auto or allo-hMSCs: 1 withdrew consent before treatment, 1 had an ICD placed prior to injection, and 1 died before treatment. The study timeline and flow of patients through the trial can be seen in Figure 6.

All allo- and auto-hMSCs were manufactured at the University of Miami Interdisciplinary Stem Cell Institute. Auto-hMSCs were obtained from participants 4-6 weeks prior to cardiac catheterizations to allow ample time for sufficient ex vivo expansion prior to transendocardial injection of participant’s own cells. Allo-hMSCs were manufactured at

Table 4: Study #3 Patient Criteria

<table>
<thead>
<tr>
<th>Patient Inclusion Criteria</th>
<th>Patient Exclusion Criteria</th>
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<tbody>
<tr>
<td>- NIDCM diagnosis with LVEF &lt; 40%</td>
<td>- LVEF &gt; 40%</td>
</tr>
<tr>
<td>- Stable for at least 3 months of LV dysfunction</td>
<td>- Patients recovering from cardiomyopathy (unstable LV dysfunction)</td>
</tr>
<tr>
<td>- LV end-diastolic diameter &gt; 5.9cm in male subjects or &gt; 5.6cm in female subjects or LV end-diastolic index &gt; 125 ml/m2</td>
<td>- Pacemaker and/or ICD placed less than 3 months prior to administration of experimental treatment</td>
</tr>
<tr>
<td>- All patients treated with appropriate maximal medical therapy for heart failure</td>
<td>- Myocarditis - excluded by endomyocardial biopsy</td>
</tr>
</tbody>
</table>

Figure 6: Flow chart of the study design

*Following screening, 37 patients were enrolled and randomized, and included for analysis of the primary endpoint, 30-day treatment-emergent serious adverse events (TE-SAES). AICD = automatic implantable cardioverter-defibrillator.*
the University of Miami Cell Production Facility from a pooled collection of donors. All allo-hMSCs donors were male, Caucasian, with a mean age of 25.4 years. Allo-hMSCs were from 11 men with a mean age of 58 years, and 6 women with a mean age of 55 years. Injections were then administered transendocardially during cardiac catheterization using the Biosense Webster MyoStar NOGA Catheter system. Injection sites for therapeutic administration were selected to distribute sites evenly throughout the accessible left ventricular myocardium and to prioritize safety of the transendocardial stem cell injection.

Prior to treatment administration, baseline assessment of all patients was performed including chemistry and hematology laboratory tests, echocardiography, and CT scans or MRI imaging of the chest, abdomen, and pelvis. Following cardiac catheterization and TESI, patients were admitted to the hospital for a minimum of 2 days and were required to follow-up post-treatment at 2 weeks and at 2, 3, 6, and 12 months for safety and efficacy evaluation. LVEF was evaluated at baseline and at 12 months. 6MWT results were evaluated at baseline, 6 months, and 12 months.

The data analysis of this open-label study masked all parties involved in statistical analysis of results. All patients who received study injection were included in analysis. “All statistical tests were performed at alpha = 0.05 using 2-sided tests.”

**Study Results**

At 12 months post-treatment, the LVEF increased in the allo-hMSC group by 8.0% (CI: 2.8% to 13.2%, p = 0.004) compared to baseline which was found to be statistically significant, but the LVEF increase of 5.4% in the auto-hMSC group was not statistically significant (CI: -1.4% to 12.1%; p = 0.116). The statistically significant increase in the allo-hMSC group resulted in the post-treatment LVEF exceeding 40% in 46.7% of the patients in this group. The auto-hMSC group post-treatment LVEF exceeded 40% in only 22.2% of patients in this group.

At 12 months post-treatment, the 6MWT distance significantly increased in the allo-hMSC treatment group by 37.0 meters (CI: 2.0m to 72.0m, p = 0.04) compared to baseline. At the same time point, the auto-hMSC treatment group 6MWT increase of 7.3 meters compared to baseline was not statistically significant (CI: -47.8m to 33.3m, p = 0.71). Figure 7 shows results of these end points.
The primary safety endpoint measured in this study was the incidence of any treatment-emergent serious adverse events (TE-SAEs) occurring within 30 days after treatment. There were no TE-SAEs observed in the first 30 days. Two deaths occurred post-injection in the auto-hMSC group, but both events were considered to be unrelated to the study treatment.

In summary, these results support clinical efficacy of transendocardial stem cell infusion of allo-hMSCs in the setting of nonischemic dilated cardiomyopathy since a statistically significant improvement from baseline was seen in the allo-hMSC group in LVEF and 6MWT, indicating that a significant improvement of functional capacity in these patients with NIDCM was achieved as a result of this experimental therapy. If results of this clinical trial are replicated in a larger randomized control trial, TESI of allo-hMSCs could be considered as a therapeutic option to improve functional capacity in patients with NIDCM.

**Study Critique**

Strengths of this study include the stringent inclusion and exclusion criteria used to select study participants, including all patients who received either treatment in the final data analysis, and consistency with location of stem cell collection and culture. This study is hampered by a very small sample size at a single hospital center, lack of a placebo group (by trial design), and loss of patients due to withdrawal of consent or loss to follow-up. The trial sample size was determined prospectively based on predicted rates of serious adverse events, and, although the sample size is too small to draw concrete conclusions regarding efficacy of therapy, the findings are valuable in designing future studies.

It is important to note that the mean age of the stem cell donors in the allo-hMSC group was roughly one half of the mean age of the stem cell donors in the auto-hMSC group. This significant mean age difference between the stem cells used in the two treatment groups in this study could potentially account for the increased efficacy of the allo-hMSC treatment.
Implications of this difference between treatment groups include the possibility that study end points in both treatment groups would show statistically significant improvement compared to baseline if the average age of stem cell donors for the auto-hMSC group was reduced to match that of the allo-hMSC group, or that the study cannot be considered reliable due potential confounding variables resulting from this difference.

Level of Evidence: 1B

**DISCUSSION**

Nonischemic dilated cardiomyopathy is a progressive and deadly disorder with a significant global impact and only one curative treatment option at this time: a total heart transplant. Stem cell therapy in the setting of NIDCM is hypothesized to provide another curative option for this disorder as evidence shows potential for this therapy to regenerate damaged heart tissue, in turn increasing functional capacity and, therefore, quality of life.

End point measurements of cardiac improvement after stem cell therapy being evaluated in this paper include the 6-minute walk test (6MWT) and left ventricular ejection fraction (LVEF). The 6MWT is frequently used to determine functional capacity in patients with heart failure. In this test, the patient is asked to walk, self-paced, back and forth between 2 marked points on a flat surface for 6 minutes. Rests are allowed and the total number of meters walked at the 6-minute mark is calculated. A review paper has shown that the 6MWT is a reliable and valid test for estimating functional capacity in patients with heart failure, as the test was between 83% and 91% accurate in predicting peak oxygen uptake (VO2) when total distance walked was less than 490 meters, with VO2 being universally accepted as a measurement for functional capacity. LVEF is defined as the percent volume that is ejected during systole from the left ventricle. LVEF has been the primary parameter used in the diagnosis, management, and both symptom severity and outcome predictor in patients with heart failure. This review focuses on recent evidence that stem cell therapy causes short term improvement in the 6MWT and LVEF in the setting of nonischemic dilated cardiomyopathy.

Overview of details and results of the three studies evaluated in this paper are summarized in Table 5. Sample sizes of all three studies are too small to draw definitive conclusions from results and the small sample sizes combined with the stringent inclusion and exclusion criteria lead to restricted demographics in the studies. All three studies show significant short-term improvement in 6MWT results and two of the three studies show significant short-term improvement in LVEF after treatment with stem cell therapy, supporting
the theory that stem cell therapy may stimulate regeneration of healthy heart tissue. This suggests that larger scale future studies should be done to validate the results from these three trials.

While all three studies include patients with nonischemic dilated cardiomyopathy and evaluate safety and efficacy endpoints including LVEF and 6MWT, the specific type of stem cell, delivery method, and follow-up time points vary greatly between the three studies. Butler et al. was unique in that it is the first published experiment with intravenously-administered stem cells in patients with any type of chronic cardiomyopathy. Vrtovec et al. is the first clinical study investigating the effects of repetitive transplantation of CD34+ cells in patients with NIDCM, although repetitive treatment administration was not associated with improved clinical response except for a noticeable increase of myocardial viability in certain subsets of patients. Hare et al. is the first study comparing allogeneic and autologous human mesenchymal stem cells in the treatment of NIDCM.

Results regarding safety and efficacy of treatment in all three studies, in spite of differences in stem cell type and delivery method, showed no life-threatening adverse effects or concerns for patient safety. We assume that there were minor adverse side effects (i.e. pain from bone marrow harvesting for auto-stem cell donors), but these studies only focused on serious, short-term, and life-threatening adverse outcomes. This focus is appropriate for early phase human trials, but future studies will be needed to further evaluate life-threatening adverse events as well as other safety endpoints. Of note, it will be difficult to interpret data regarding any adverse effects that arise after a significant amount of time has passed post-stem cell treatment of NIDCM, since the morbidity and mortality of NIDCM is so high without treatment.

An important aspect of this experimental therapy to consider is the cost of treatment. The current accepted bridging therapy to heart transplantation for NIDCM is the use of left ventricular assist devices (LVAD), which cost several hundred thousand dollars to place and, more often than not, require the patient to remain hospitalized while the LVAD is in place. Many insurances do cover at least a significant portion of the cost of the LVAD when it is needed and Medicare is currently in the progress of including LVAD costs in their coverage; however, the device itself and the hospitalization it requires results in significant medical costs to both the patient and insurance companies. Stem cell therapy for NIDCM is still in experimental stages and the total cost of therapy is not known at this time, but it is estimated to be extremely expensive due to the complexity and novelty of the procedures required to obtain, expand, and administer the stem cells colonies. The LVAD has been proven to be an effective bridging option for NIDCM patients awaiting heart transplantation, whereas stem cell therapies only
appear to increase quality of life during brief short-term periods after treatment. Additionally, repeat stem cell treatments only seem to improve longer term outcomes for a very small subset of patients. At this time, it will be necessary to find a way to prolong the effects of stem cell therapy in the setting of NIDCM in order for it to be considered an effective bridging therapy option for heart transplant candidates. Stem cell therapy could, however, be effective in patients with advanced NIDCM who are not candidates for heart transplantation. This treatment could help improve their quality of life, and, hopefully, as this technology improves and advances, the stem cell therapy could regenerate healthy myocardium, potentially reversing the effects of the disease and further improving quality of life, as well as prolonging life.

The only potential bias noted in any study evaluated in this paper was involvement of several authors from Study #1 (Butler et al.) with CardioCell, which is a global biotechnology company that explores therapeutic applications of unique patented ischemia-tolerant mesenchymal stem cells (itMSCs) manufactured under cGMP conditions. CardioCell has an exclusive worldwide license from Stemedica Cell Technologies Inc. for the exploration of therapeutic cardiovascular indications, including acute myocardial Infarction (AMI), chronic heart failure (CHF), and peripheral artery disease (PAD).

Table 5: Overview of Studies

<table>
<thead>
<tr>
<th></th>
<th>Butler et al.</th>
<th>Vrtovec et al.</th>
<th>Hare et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants who were randomized into follow up</td>
<td>22</td>
<td>60</td>
<td>37</td>
</tr>
<tr>
<td>Number of participants who completed follow up</td>
<td>22</td>
<td>57</td>
<td>27</td>
</tr>
<tr>
<td>Treatment</td>
<td>Intravenous Allogenic ischemia-tolerant mesenchymal stem cell therapy (itMSCs)</td>
<td>Group A - Single Dose Transendocardial CD34+ Cell therapy + baseline G-CSF (10ug/kg, 5 days)</td>
<td>Transendocardial injection of ALLOGENIC mesenchymal stem cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group B - 0 and 6 month doses Transendocardial CD34+ Cell therapy + baseline G-CSF (10ug/kg, 5 days)</td>
<td>Transendocardial injection of AUTOLOGOUS mesenchymal stem cells</td>
</tr>
<tr>
<td>Follow up</td>
<td>0-90 days, 90-180 days</td>
<td>0 - 6 months</td>
<td>6 months - 12 months</td>
</tr>
<tr>
<td>6 Minute Walk Test treatment - control, in meters (p value)</td>
<td>36.47 (0.02)</td>
<td>A (87+/-.21) p value 0.03</td>
<td>A (27+/-.11) p value 0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B (92+/-.25) p value 0.02</td>
<td>B (12+/-.18) p value 0.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37m (pvalue 0.04)</td>
<td>7.3m (pvalue 0.71)</td>
</tr>
<tr>
<td>LVEF% (p value)</td>
<td>0.01 (0.99)</td>
<td>A (6.9+/-.3.3) p value 0.001</td>
<td>A (2.1+/-.2.3) p value 0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B (7.1+/-.3.5) p value 0.001</td>
<td>B (0.8+/-.3.1) p value 0.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8% (pvalue 0.004)</td>
<td>5.4% (pvalue 0.116)</td>
</tr>
</tbody>
</table>
CONCLUSION

Stem cell therapy is shown to be safe, well-tolerated, and effective in improving functional capacity, quality of life, and short-term event survival in patients with nonischemic cardiomyopathy. All three studies displayed short-term improvements in LVEF and/or 6MWT, with a small sample size. No major adverse events were attributed to the interventions. Further randomized controlled trials are warranted in order to validate long-term results in a larger population before a clinical recommendation can be given; however, because of these positive results and potential therapeutic effect, large institutions will likely be willing to fund future studies. Further research should be done to explore the hypothesis that the positive findings are a result of immunomodulatory factors stimulated by the act of transplantation, rather than the stem cells, exclusively. If this is the case, a more cost-effective synthetic injection could likely be created to stimulate the same response, limiting the need to harvest human stem cells. In conclusion, stem cell therapy is a promising alternative therapeutic option for patients with nonischemic cardiomyopathy.

ACKNOWLEDGEMENTS

We would like to thank Dr. Abby Massey, Carolyn Schubert, and the JMU Communication and Writing Centers for their assistance with this project.
References


