A Pilot Trial to Assess Potential Effects of Selective Intracoronary Bone Marrow-Derived Progenitor Cell Infusion in Patients with Non-Ischemic Dilated Cardiomyopathy: Final 1-Year Results of the TOPCARE-DCM Trial

Fischer-Rasokat et al.: Cell therapy in non-ischemic DCM

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Total word count: 5897

Subject Codes: congestive heart failure, catheter based coronary and valvular interventions: other, angiogenesis, other vascular biology

Clinical Trial Registration Information: Clinicaltrials.gov number NCT00284713
Abstract

Background Intracoronary administration of bone marrow-derived progenitor cells (BMC) was shown to improve coronary microvascular function in ischemic heart disease. Since coronary microvascular dysfunction is implicated in the pathogenesis and prognosis of non-ischemic dilated cardiomyopathy (DCM), we investigated the effects of intracoronary BMC administration in patients with DCM.

Methods and Results Intracoronary infusion of BMC was performed in 33 patients with DCM by an over-the-wire balloon catheter. Left ventricular (LV) contractility at baseline and after three months was assessed by analysis of LV angiograms. Coronary hemodynamics were determined by intracoronary Doppler wire measurements. After three months, regional wall motion of the target area (contractility from -1.08±0.39 to -0.97±0.47 SD/chord, p=0.029) and global LV ejection fraction (from 30.2±10.9 to 33.4±11.5 %, p<0.001) were improved. Increase of regional contractile function was directly related to the functionality of the infused cells as measured by their colony forming capacity. Minimal vascular resistance index was significantly reduced in the BMC-treated vessel after three months (from 1.53±0.63 to 1.32±0.61 mmHg*s/cm; p=0.002, n=24), whereas no changes were observed in the reference vessel (from 1.60±0.45 to 1.49±0.45 mmHg*s/cm; p=0.133, n=13). 12 months after BMC infusion, NT-proBNP serum levels were decreased suggesting a beneficial effect on LV remodeling processes (from 1610±993 to 1473±1147 pg/ml; p=0.038 for logNT-proBNP, n=26).

Conclusions Intracoronary administration of BMC appears to be associated with improvements in cardiac contractile and microvascular function in patients with DCM. Thus, randomized blinded studies are warranted to evaluate potential clinical benefits of intracoronary BMC administration in patients with DCM.

Keywords cardiomyopathy, cells, catheterization, myocardial contraction, regional blood flow
Introduction

Severely reduced coronary flow reserve and impaired microvascular function have been demonstrated in patients with non-ischemic dilated cardiomyopathy (DCM) [1, 2]. The degree of coronary microvascular dysfunction has been shown to be an independent predictor of cardiac events such as death or further progression of heart failure [3]. Recent elegant experimental studies additionally provided convincing evidence for the crucial role of coordinated angiogenesis to prevent the progression from adaptive cardiac hypertrophy to heart failure in the absence of epicardial flow-limiting stenosis [4, 5]. In fact, inhibition of angiogenesis led to decreased capillary density and profound systolic dysfunction [4, 5], whereas promoting cardiac angiogenesis by introducing angiogenic factors or genetic silencing of anti-angiogenic molecules restored cardiac function [5, 6]. These experimental observations shed new light on the long known and well established association between coronary microvascular dysfunction and dilated cardiomyopathy in the absence of epicardial artery atherosclerosis (for review see [7]).

Clinically, therapeutic interventions to improve coronary microvascular dysfunction in the absence of epicardial artery flow-limiting stenoses are very limited [7]. However, recent experimental and clinical studies indicated that either intracoronary or intramyocardial administration of bone marrow-derived progenitor cells (BMC) may contribute to increased neovascularization and stimulated angiogenesis in ischemic tissue [8-11]. Moreover, two recent placebo-controlled clinical trials demonstrated that the administration of either blood- or bone marrow-derived progenitor cells into the coronary artery supplying both acute as well as chronic myocardial infarction was associated with significant improvements in coronary microvascular function and vascular conductance capacity [12, 13]. However, it is unknown, whether such a treatment strategy may also affect coronary vascular function in patients with DCM.

Therefore, we initiated the Transplantation Of Progenitor Cells And functional Regeneration Enhancement pilot trial in patients with non-ischemic Dilated CardioMyopathy (TOPCARE-DCM). The primary hypothesis to be tested was, whether selective intracoronary infusion of
BMC may be associated with measurable improvements in target area contractility in patients with global left ventricular (LV) hypokinesia in the absence of obstructive epicardial coronary artery disease.
Methods

Patients

33 patients with DCM were recruited into the study. Patients between 18 and 80 years of age were eligible for inclusion into the study, if global ejection fraction (LVEF) was < 40% and LV end diastolic diameter was > 60 mm, both determined by echocardiography. Moreover, patients had to be in a stable clinical condition within the last 6 months with a fixed pharmacological therapy. Exclusion criteria were a history of myocardial infarction, a coronary intervention in the past or a history of other severe chronic diseases or cancer. The ethics review board of the Goethe University in Frankfurt, Germany, approved the protocol; the trial was registered according to the German Drug Law and with Clinicaltrials.gov number NCT00284713. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Study Design

This prospective, open-label study consisted of an initial cell therapy and two follow-up visits scheduled after 3 and 12 months. Cardiac catheterization was performed initially and after 3 months. The primary end point of the study was the absolute change in regional LV wall motion of the target area as measured by quantitative angiography 3 months after cell administration. Secondary end points included quantitative variables relating to LVEF, LV volumes, coronary flow reserve, and serum NT-proBNP levels after 12 months.

Preparation of progenitor cells

50 ml of bone marrow aspirate were obtained under local anesthesia in the morning of the cell transplantation day. BMC were isolated by Ficoll density gradient centrifugation as previously reported [14]. The number of infused BMC was 259 ± 135 *10^6. The functional capacity of the infused BMC was determined by measuring their colony forming unit capacity (CFU), as described previously [14].
Catheterization Procedure for Progenitor Cell Transplantation

The target vessel used for subselective intracoronary BMC administration was the left anterior descending artery (LAD) in 21 patients and the left circumflex artery (LCX) in one patient, where the LAD could not be selectively wired for advancing the infusion balloon. In additional 11 patients of the TOPCARE-DCM-extended protocol, both the LAD and the LCX were used for cell administration, each receiving 5 ml of the 10 ml cell suspension. Cells were infused using the stop-flow technique as described [15]. After completion of intracoronary cell transplantation, coronary angiography was repeated to ascertain vessel patency and unimpeded flow of contrast material.

Left Ventricular Angiography

LV angiograms in RAO and LAO projections were obtained at the time of the baseline procedure immediately prior to intracoronary BMC administration and at 3 months follow-up in identical radiographic projections. Quantitative analysis of paired LV angiograms in RAO-projections was performed by the area-length method and by the centerline method with QCA-CMS software (version 6.0, Medis), as described elsewhere [15]. The myocardial target region was defined as the LV circumference in RAO projection supplied by the coronary arteries used for BMC infusion to the distal end of the angiographically visible coronary artery territory. The extent of LV hypokinetic area was defined as percent circumference of hypokinetic chords [% circumference]; the severity of LV hypokinesia was defined as the area under the curve given by chords with a contractility < 1SD [AUC], contractility of the target area was defined as the mean value of regional standard deviations per analyzed chords [SD/chord].

Magnetic Resonance Imaging

In a subgroup of 9 patients, who did not have implanted defibrillators or pacemakers and who consented to and tolerated the imaging procedure, cardiac magnetic resonance imaging
(MRI) (a 1.5-T system; Magnetom Sonata, Siemens Medical Solutions) was performed at baseline and at 3 months' follow-up. MRI sequences were analyzed by an experienced investigator as previously reported [16].

Measurement of Coronary Flow Reserve

Paired recordings of Doppler-derived coronary blood flow (CBF) velocities in the target vessel (LAD in all patients) as well as in the reference vessel (LCX in 13 of the 24 patients having serial CBF measurements) with sufficient quality for quantitative analysis were obtained in 24 patients both at baseline as well as at 3 months follow-up. CBF was assessed with the use of an intracoronary Doppler wire as previously described [17]. Basal average peak velocity was registered after administration of nitroglycerin, and coronary flow reserve was assessed after induction of maximal blood flow by intracoronary infusion of 2.4 mg/min adenosine, similar to the protocol used by Cox et al. [18]. Three months after progenitor cell therapy, cardiac catheterization was repeated to measure coronary flow reserve in both the target and the reference artery at identical sites as during the initial examination.

Parameters of Coronary Flow

Volumetric blood flow at baseline or hyperemic conditions was calculated as 0.125 * \( \pi \) * average peak velocity (APV, basal or following adenosine infusion) * square of inner lumen diameter of the coronary artery [17]. Lumen diameter immediately distal to the Doppler tip was determined by quantitative coronary angiography as previously described [17]. Basal and minimal coronary vascular resistance indices were calculated as mean arterial pressure divided by APV measured by the Doppler wire at baseline and during adenosine-induced maximal coronary vasodilatation, respectively. Coronary flow reserve (CFR) of the target vessel and the reference vessel was computed as the ratio of adenosine-induced APV and APV at baseline [13].

Evaluation of Safety and Feasibility
Clinical, laboratory, and safety-related data were prospectively collected. Follow-up visits were performed after 3 months (mean time after initial cell therapy 3.5 ± 1.5 months, median 3) and after 12 months (12.8 ± 1.7 months, median 12). Procedural complications were defined as any new-onset ventricular arrhythmia, visible thrombus formation, distal embolization, or injury of the coronary artery associated with the cell-infusion catheterization procedure. 24-hours holter-monitoring was performed for each patient at the 12 months follow-up visit. Three patients received a second cell therapy after the 3 months follow-up. However, as follow-up visits in our clinic were continued, safety-data, adverse events and NT-proBNP serum levels at the 12 months follow-up visit of these patients are included into this analysis.

**Measurement of NT-proBNP**

Blood for serum analysis was collected from each patient at the day of cell therapy and at 12 months follow-up, and the serum levels of NT-proBNP in pg/ml were determined using a 1-step enzyme-immunoassay (Elecsys 2010, Roche Diagnostics). Statistical analysis was performed after logarithmic transformation of NT-proBNP values.

**Statistical Analysis**

Continuous variables are presented as means (±SD), unless otherwise noted. Categorical variables were compared with use of the chi-square test. Statistical comparisons between initial and follow-up data were performed in a nonparametric, paired fashion with use of the Wilcoxon signed-rank test. We used nonparametric Spearman-correlation for univariate analysis. Statistical significance was assumed if p<0.05. All reported p values are 2-sided. Statistical analysis was performed using SPSS for Windows version 15.0 (SPSS Inc., Chicago, Illinois).
Results

Patient characteristics
The baseline characteristics of the patient population are summarized in table 1. All patients were in stable condition with respect to symptoms and medication for heart failure for at least 6 months prior to inclusion into the study. Heart failure was diagnosed at a median of 86 months prior to study therapy. The majority of patients were in NYHA class II indicating an only modest severity of heart failure at baseline. In those patients with documented myocarditis, the most recent diagnosis of inflammatory infiltration of the myocardium was obtained between 36 and 173 months before BMC administration. Patients were on chronic (>6 months) maximal pharmacological therapy for heart failure.

Procedural characteristics
There were no procedure-related complications during intracoronary instrumentation and BMC administration. In 4 of the 33 patients (=12%) troponin T levels increased from below detection limit (<0.01 ng/ml) to 0.02 in two patients and to 0.03 and 0.04 ng/ml, respectively, in two additional patients 24 hours after BMC administration. Two patients had slightly elevated troponin T levels of 0.02 and 0.07 ng/ml already at baseline prior to cell administration. At 3-months angiographic follow-up, none of the patients demonstrated wall irregularities or stenosis at the site of the previous balloon inflation. There was no death, myocardial infarction or stroke up to 1 year follow-up. Within the 1 year follow-up period, none of the patients revealed ventricular arrhythmias necessitating the implantation of an implantable cardioverter defibrillator despite extensive 24-hours holter monitoring.

Effects of BMC administration on quantitative parameters of left ventricular function
Subselective administration of BMC was associated with significantly (p=0.029) increased contractility of the LV area supplied by the coronary arteries used for BMC administration and, thus, targeted by potential therapeutic effects, as measured by improved wall motion.
from -1.08 ± 0.39 prior to cell administration to -0.97 ± 0.47 SD/chord at 3 months angiographically follow-up. In contrast, wall motion did not change in the non-targeted segments of the left ventricle (p=ns. for the chords of the non-targeted area). In parallel with the increase in target-area regional wall motion, both the extent of LV hypokinesia (figure 1A) as well as the severity of LV hypokinesia (figure 1B) were significantly reduced. Overall, LVEF increased by an absolute 3.2 ± 4.1 percentage points (figure 1C), whereas the increase relative to baseline LVEF was 12.8 ± 19.1 % (p<0.001). Patients with a history of active myocarditis (n=4) did not differ in their changes in LVEF (from 25.5 ± 12.7 to 29.8 ± 15.4 %; relative increase 15.4 ± 12.4 %) compared to the entire study cohort.

Endsystolic LV volumes demonstrated a nonsignificant trend to decrease from 81 ± 42 ml/m² of body surface area (BSA) at baseline to 76 ± 38 ml/m² of BSA at 3 months follow-up (p=0.050), whereas enddiastolic LV volumes remained unchanged (113 ± 45 ml/m² of BSA vs. 109 ± 40 ml/m² of BSA; p=0.288).

In the 9 patients with serial cardiac MRI suitable for quantitative analysis, MRI-derived LVEF increased from 32.3 ± 9.2 to 36.7 ± 9.7 % (p=0.011), endsystolic LV volumes showed a trend to decrease from 90 ± 53 ml/m² to 76 ± 50 ml/m² of BSA (p=0.066), and enddiastolic LV volumes remained unchanged (127 ± 61 ml/m² at baseline vs. 114 ± 56 ml/m² of BSA at follow-up; p=0.110). Thus, MRI-derived LV functional analysis in a small subset of patients without pacemakers/defibrillators corroborated the data obtained by quantitative LV angiographic analysis.

Finally, as illustrated in figure 2, there was a significant correlation between the number of hematopoietic colonies formed by the BMC used for administration and the absolute decrease in the extent of LV hypokinesia suggesting a potential relation between the functionality of the infused cells (as measured by their CFU capacity) and the increase of regional contractile function 3 months after BMC administration. However, there was no correlation between CFU capacity and changes in global LV function, as measured by LVEF or the number of segments displaying hypokinesia.
Effect of BMC administration on coronary blood flow parameters

Paired serial assessments of CBF by intracoronary Doppler measurements in the BMC-infused coronary artery were suitable for quantitative analysis in 24 patients at both baseline and at 3 months follow-up. The rate-pressure product (7942 ± 2238 vs. 7481 ± 1530 mmHg/min; p=0.331) as well as the coronary artery luminal diameters of the target vessel (2.8 ± 0.7 vs. 2.8 ± 0.7 mm; p=0.864) did not differ between the initial measurement immediately prior to BMC administration and at 3 months follow-up. At 3 months follow-up, basal CBF in the BMC-treated vessel was unchanged (from 50 ± 20 to 53 ± 24 ml/min, p=0.549). However, adenosine-induced maximal blood flow showed a trend to increase from 176 ± 84 ml/min prior to BMC administration to 204 ± 101 ml/min at 3 months follow-up (p=0.063) in the BMC-treated vessel. Adenosine-induced minimal vascular resistance was significantly reduced in the BMC-treated vessel (1.53 ± 0.63 vs. 1.32 ± 0.61 mmHg*s/cm; p=0.002, figure 3). In contrast, in the 13 patients receiving BMC subselectively into the LAD, but not in the LCX, neither adenosine-induced maximal blood flow (176 ± 87 vs. 176 ± 78 ml/min, p=0.600) nor adenosine-induced minimal vascular resistance (1.60 ± 0.45 vs. 1.49 ± 0.45 mmHg*s/cm; p=0.133) changed in the untreated reference vessel, while basal blood flow slightly, but nonsignificantly increased (40 ± 20 vs. 49 ± 18 ml/min, p=0.060). However, as illustrated in figure 3, the individual changes in minimal vascular resistance indices from baseline to 3 months after progenitor cell therapy demonstrated a considerable variability. Moreover, there were no associations between baseline-parameters or cell characteristics and changes in coronary hemodynamics. Likewise, changes in coronary hemodynamics did not correlate with changes in regional or global LV function parameters.

Effects of BMC administration on NT-proBNP serum levels as an objective marker of cardiac function
Analysis of NT-proBNP serum levels one year after BMC administration could be performed in 26 patients. Three patients presented with de novo atrial fibrillation or renal failure at 12 months follow-up rendering NT-proBNP measurements meaningless and four patients refused blood sampling at 12 months follow-up. NT-proBNP serum levels significantly decreased from 1610 ± 994 prior to study inclusion to 1473 ± 1147 pg/ml (p=0.038 vs. baseline for logNT-proBNP) 12 months after progenitor cell administration. The decrease in NT-proBNP serum levels did not correlate with CBF changes or with cell characteristics.
Discussion

The results of the present study suggest that, in patients with DCM, the selective intracoronary administration of BMC into one of the three coronary arteries may be associated with a measurable improvement of regional wall motion of the LV segments targeted by intracoronary cell administration, which appears to translate into an improved global LV pump function at 3 months and an increased overall cardiac performance as measured by reduced NT-proBNP serum levels at 12 months past cell therapy. The improvement in regional contractile function appears to be directly correlated with the functional activity of the infused cells, as measured by their colony-forming capacity. Mechanistically, the administration of bone marrow-derived mononuclear cells appears to be associated with an improvement in maximal vascular conductance capacity of the coronary artery used for cell administration.

The results of this pilot study extend previous observations in patients with acute myocardial infarction [19] as well as chronic post-infarction heart failure secondary to healed myocardial infarction [20, 21]. In these previous trials, the intracoronary administration of functionally competent BMC into the infarct-related artery was not only shown to increase LV contractile function [19-21], but also to improve coronary microvascular function [12] and maximal vascular conductance capacity of the target vessel [12, 13]. A number of experimental studies have demonstrated that cellular therapeutics using various bone marrow- or blood-derived progenitor cells improve neovascularization in ischemic hindlimb or heart models in mice, rats, pigs and dogs [22-26]. Mechanistically, transplanted progenitor cells secrete a variety of proangiogenic factors [22, 27, 28], which might contribute to neovascularization and enhance endogenous cardiac repair via paracrine factors [29, 30]. Thus, the neovascularization-mediating effects may not necessarily involve the direct differentiation of transplanted cells into endothelial cells, which is still controversially discussed in humans [31]. Based on convincing experimental evidence that stimulation of coronary microvascular dilator function and angiogenesis is capable to restore cardiac contractile function in models
of non-ischemic heart failure [5, 6], we hypothesized that the intracoronary administration of BMC may also improve LV function in patients with DCM, irrespective of potential, yet controversially discussed effects on cardiomyocyte regeneration.

Mechanistically, the improvement in maximal vascular conductance capacity may have contributed to the increased regional contractile function of the LV segments targeted by intracoronary cell administration. Indeed, in a recent very elegant experimental study, Hare and co-workers demonstrated that intramyocardial injection of mesenchymal stem cells led to a significant increase in tissue perfusion, which preceded improvements in regional and global LV function [24]. These data suggest that an early effect on tissue perfusion represents an important feature of subsequent functional cardiac regeneration. Disease progression from preserved LV function to progressive impairment of systolic function, ventricular dilation and overt heart failure has been demonstrated in patients with severely reduced microvascular dilator response [32]. The increase in vascular conductance capacity after BMC administration observed in the present study may mirror an increase of the cross-sectional area of the targeted vessel, suggesting neovascularization as one potential mechanism of BMC infusion. Thus, it is conceivable that improved microvascular perfusion may have contributed to the increase in cardiac performance in these patients with DCM. However, it should be noted that there was a considerable heterogeneity in individual CBF responses. Moreover, we could not detect any association between changes in coronary hemodynamics and changes in regional wall motion of the targeted LV segments. As disclosed by experimental studies, although sustained increases in tissue perfusion do not appear to be necessary for improved LV function following cell administration, increased blood flow seems to be a critically important feature of functional myocardial regeneration [24]. In fact, 8 weeks after injection of mesenchymal stem cells into a pig model of acute myocardial infarction, myocardial blood flow was similar in cell injected and control hearts, but both regional and global LV function had significantly improved only in the cell injected hearts [24]. Since coronary flow dynamics and LV function were assessed in the present
study at a single time point at 3 months after cell administration, it is possible that increases in CBF had not yet translated into the full extent of subsequent functional cardiac regeneration and, therefore, no association between the extent of contractile improvement and increased CBF could be observed. Indeed, the delayed significant reduction in NT-proBNP serum levels at one year follow-up observed in the present study suggests that LV remodeling processes continued to occur between 3 and 12 months after cell administration. Thus, additional studies at later time points are required to establish a potential association between changes in CBF and increases in contractile function.

Limitations of this study

The most important limitation of the present pilot trial is the lack of a randomized control group not receiving cell therapy. As such, we cannot exclude that potential confounders like better compliance to medication or more intense medical care in our patients included into a clinical trial may have affected the results. Although the selective infusion of the cells into a single coronary artery using the non-infused coronary artery as an intra-patient reference vessel in 22 patients, of whom 13 had assessment of coronary flow dynamics, as well as regional analysis of LV function of the segments targeted by the coronary artery used for cell administration does allow for correlating potential effects on LV function with the cell distribution, we cannot exclude that global LV functional parameters and, most importantly, NT-proBNP serum levels as objective markers of global LV remodeling have been affected by confounding factors. In addition, we did not use the right coronary artery for cell administration primarily for safety reasons. Thus, we cannot comment on whether therapeutic effects would be increased, when all regions of the left ventricle receive cells. Finally, in the present study, we used the intracoronary route of cell administration. As such, any potential effect of cell therapy requires the extravasation of cells into the myocardial tissue. Previous studies have demonstrated acute cell retention rates in the heart as measured by Indium-111 labelling and total body scanning ranging from 1-19% of the applied cells following intracoronary administration, with the highest values observed in patients with
acute myocardial infarction and lowest values in patients with healed scar tissue more than 6 years after myocardial infarction [33]. Since patients with DCM do not have acute ischemic myocardial injury, the cell retention rate in the present study is anticipated to be in the lower range between 1-5% of all applied cells. Given that previous studies have demonstrated significant increases in regional contractile LV function and perfusion by directly injecting bone marrow- or blood-derived progenitor cells into the myocardium [9-11, 34, 35], it will be important to address the question whether direct intramyocardial cell injection is superior to the intracoronary route of application, specifically in patients with non-ischemic heart failure. Likewise, the association between cell functionality and the extent of increase in contractile function observed in the present study may not be relevant, when cells are directly injected into the myocardium. Clearly, any cohort of patients diagnosed with DCM will consist of a variety of different etiologies, including primary and secondary cardiomyopathies [7]. Although we excluded patients with clinical and/or bioptic evidence of acute myocarditis, there was a considerable heterogeneity in the response of individual patients. However, the number of investigated patients is too small to address any potential difference in the response to intracoronary cell administration with respect to the etiology of the cardiomyopathy.

In summary, the results of the present pilot study in patients with DCM may indicate that the intracoronary administration of functionally competent BMC is associated with measurable improvements in contractile function of the targeted LV segments and with a modest reduction in NT-proBNP serum levels. Based on the excellent safety profile, the results of the present pilot study provide the rationale to design a randomized blinded trial in order to evaluate potential clinical benefits of intracoronary BMC administration in patients with DCM.
Acknowledgements

We greatly appreciate the enthusiastic support of the staff of our catheterization laboratories and by our technicians Isabel Geweyer, Beate Mantz, Heike Wagner, Marga Müller-Ardogan, Stephanie Estel (study nurses) and Tina Rasper, Tino Röxe (biological technicians).

Funding

The study was supported by the Deutsche Forschungsgemeinschaft (FOR 501-1:WA146/2-1), by the Foundation Leducq Transatlantic-Network-of-Excellence-for-Cardiac-Regeneration, by the European-Vascular-Genomics-Network (http://www.evgn.org; contract number LSHM-CT-2003-503254), and by the Alfred-Krupp-Stiftung (SD).

Conflict of Interest

Dr. Dimmeler reports being a member of the scientific advisory board of Guidant. Dr. Zeiher reports having received consulting fees from Guidant. Drs. Dimmeler and Zeiher report that they are cofounders of t2cure, a for-profit company focused on regenerative therapies for cardiovascular disease. They serve as scientific advisors and are shareholders.
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Figure legends

Figure 1
Individual changes of the extent of hypokinetic area (A), severity of hypokinesia (B) and ejection fraction (C) between baseline and 3 months follow-up.

Figure 2
Correlation between the absolute decrease in the extent of left ventricular hypokinesia between baseline and 3 months follow-up and the functionality of the infused cells, given by the number of hematopoietic colonies formed out of 100000 of each patient's BMC.

Figure 3
Individual changes of the adenosine-induced minimal vascular resistance index of the BMC-treated LAD for all 24 patients between baseline and 3 months follow-up.
Table 1: Baseline characteristics of the patients

**Demographic characteristics**

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<td>Number of patients</td>
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</tr>
<tr>
<td>Age – yr</td>
<td>56 ± 11</td>
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<td>Female sex – no.(%)</td>
<td>8(24)</td>
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<td>NYHA class I/II/III – no.(%)</td>
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**Medical history**

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<td>Time since first clinical manifestation of heart failure – mo(median)</td>
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<td>Previous Myocarditis - (mo before cell treatment)</td>
<td>4 (36/70/104/173)</td>
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<td>Pacemaker / implantable cardioverter-defibrillator – no.(%)</td>
<td>4(12)/13(39)</td>
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**Current Medication**

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<td>Beta-blocker – no.(%)</td>
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<tr>
<td>ACE-inhibitor or angiotensin-receptor blocker – no.(%)</td>
<td>31(94)</td>
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<tr>
<td>Spironolactone – no.(%)</td>
<td>26(79)</td>
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<tr>
<td>Diuretics – no(%)</td>
<td>33(100)</td>
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<tr>
<td>Digitalis – no.(%)</td>
<td>21(64)</td>
</tr>
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Figure 1

A

Extent of hypokinetic area

\[ p = 0.001 \]

62.1 ± 18.3

Baseline

55.9 ± 20.9

3 months FUP

B

Severity of hypokinesia (Area < -1)

\[ p = 0.019 \]

76.6 ± 35.5

Baseline

70.1 ± 36.1

3 months FUP

C

Ejection Fraction

\[ p < 0.001 \]

30.2 ± 10.9

Baseline

33.4 ± 11.5

3 months FUP
Figure 2

Hematopoietic colonies [no.]

Δ Hypokinesia [AUC]

from baseline to 3 months FUP

$r = -0.45, p = 0.009$
Figure 3

Minimal vascular resistance index
of the target vessel

Baseline 3 Months FUP

[mmHg x s/cm]

1.53 ± 0.63 1.32 ± 0.61

p=0.002
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Circ Heart Fail. published online July 29, 2009;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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