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Intramyocardial bone marrow mononuclear cell transplantation in ischemic heart failure: Long-term follow-up

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BACKGROUND: Long-term results regarding treatment of chronic ischemic heart failure with bone marrow mononuclear cells (BMMCs) have been few. We received encouraging results at the 1-year follow-up of patients treated with combined coronary artery bypass grafting (CABG) and BMMCs, so we decided to extend the follow-up.

METHODS: The study patients had received injections of BMMCs or vehicle into the myocardial infarction border area during CABG in a randomized and double-blind manner. We could contact 36 of the 39 patients recruited for the original study. Pre-operatively and after an extended follow-up period, we performed magnetic resonance imaging, measured pro-B-type amino-terminal natriuretic peptide, reviewed patient records from the follow-up period, and determined current quality of life with the Medical Outcomes Study Short-Form 36 (SF-36) Health Survey.

RESULTS: The median follow-up time was 60.7 months (interquartile range [IQR], 45.1–72.6 months). No statistically significant difference was detected in change of pro-B-type amino-terminal natriuretic peptide values or in quality of life between groups. The median change in left ventricular ejection fraction was 4.9% (IQR, –2.1% to 12.3%) for controls and 3.9% (IQR, –5.2% to 10.2%) for the BMMC group ($p = 0.647$). Wall thickening in injected segments increased by a median of 17% (IQR, –5% to 30%) for controls and 15% (IQR, –12% to 19%) for BMMC patients ($p = 0.434$). Scar size in injected segments increased by a median of 2% (IQR, –7% to 19%) for controls but diminished for BMMC patients, with a median change of –17% (IQR, –30% to –6%; $p = 0.011$).

CONCLUSIONS: In the treatment of chronic ischemic heart failure, combining intramyocardial BMMC therapy with CABG fails to affect cardiac function but can sustainably reduce scar size, even in the long-term.

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During the past decade, multiple trials have investigated effects of bone marrow mononuclear cells (BMMCs) in the treatment of chronic ischemic heart disease and acute myocardial infarction. Despite promising findings in animal trials,[1,2] clinical trials have failed to show unequivocal

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results. Furthermore, follow-up times have been almost invariably quite limited, ranging from 4 to 18 months.

Between 2006 and 2011, we conducted a randomized, double-blinded clinical trial (ClinicalTrials.gov Identifier: NCT00418418) investigating the safety and efficacy of BMMC transplantation as an adjunct to coronary artery bypass graft (CABG) surgery.[3] Initially, follow-up was 1 year post-operatively. According to our results, BMMCs seemed to have no effect on global or local left ventricular (LV) function, but the scar size was significantly diminished in the BMMC-treated areas compared with placebo.

Encouraged by this result, we decided to continue the study and invited our patients for a late follow-up visit. As in the pre-operative assessment, LV function and scar size were analyzed by cardiac magnetic resonance imaging (MRI). In addition, we measured the circulating pro-B-type amino-terminal natriuretic peptide (proBNP) concentration, determined the current New York Heart Association (NYHA) Functional Classification, and used the Medical Outcomes Study Short-Form 36 (SF-36) Health Survey to assess the post-operative health-related quality of life (HRQoL). In this report we document the long-term results of intramyocardial BMMC injections combined with CABG using randomized double-blinded techniques.

Methods

This study was approved by the Institutional Ethics Committee (Dnro HUS 456/E6/05).

Patients

The original study protocol and the 1-year follow-up results of our trial have been published previously.[3] Patients were included in the original trial if they met the following inclusion criteria: age between 18 and 75 years, provided informed consent, LV ejection fraction (LVEF) between $\leq 45\%$ and $\geq 15\%$, and NYHA class II to IV heart failure symptoms. Criteria for exclusion were:

A. heart failure due to LV outflow track obstruction;
B. history of life-threatening ventricular arrhythmias or resuscitation, or insertion of implantable cardioverter-defibrillator (ICD);
C. stroke or other disabling condition within 3 months before screening;
D. severe valve disease;
E. other serious disease limiting life expectancy;
F. contraindications for coronary angiogram or MRI; or
G. participation in another clinical trial.

Eligible patients received optimal pre-operative medication for heart failure and coronary disease for a minimum of 4 weeks, after which the screening echocardiogram was repeated. If the LVEF was still $\leq 45\%$, the patient was included in the study after informed consent, and a CABG operation was scheduled, with pre-operative studies performed during the waiting period.

Procedure

Bone marrow aliquots (100 ml) were harvested from all patients from the posterior iliac crests under anesthesia before surgery. The mononuclear cell fraction was obtained by standard methods of Helsinki University Meilahti Hospital Cell Processing Laboratory.[3] The cell suspension was divided into six 1-ml syringes for the treatment group; control patients received only vehicle medium by syringes. The patients were assigned randomly, and the syringe contents were masked to ensure double-blinded technique.

After the bone marrow aspiration, a standard CABG operation was performed. After the bypass anastomoses were finished and the heart remained in cardiac arrest, the BMMCs were injected into pre-defined sites in the infarction border area. The infarction and its border area were localized pre-operatively by imaging data, and this information was used to target the injections to the border area during surgery. The injection procedure was carefully photographed during the procedure, and the areas injected were specified in patient documents for analysis.

Follow-up

After the original 1-year follow-up, patients were monitored in the outpatient clinic of Helsinki University Central Hospital or in a regional health center according to local routines. In Spring 2013, the patients were invited for a late follow-up research visit at our institution. For end point measures in this long-term follow-up, we determined (1) changes in the LV measurements and scar size between the pre-operative and late post-operative MRI studies, (2) concomitant changes in NYHA class and plasma proBNP concentration; (3) hospitalizations due to cardiac failure, and (4) the patients' current HRQoL by the SF-36 questionnaire. The SF-36 is a standardized questionnaire with specified mean and standard deviation (SD) values for 8 different dimensions of the instrument per different cohorts that reflect (1) physical functioning; (2) role-physical, measuring role limitations because of physical health problems; (3) role-psychological, assessing role limitations as a result of emotional impairment; (4) vitality, assessing the feeling of energy or fatigue; (5) mental health; (6) social functioning, measuring ability to perform normal social activities; (7) bodily pain; and (8) subjective general health perceptions. The investigator transformed the scores for each dimension to a 0- to 100-point scale for comparisons between groups. A lower score means greater limitations to activities or more distress with social and emotional problems. As a reference, we used values for a Finnish cohort with any chronic disease and compared their SF-36 mean scores with the scores of our study patients.

Cardiac MRI

Cardiac MRI was performed with a 1.5-T Sonata scanner and phase-array cardiac coil (Siemens AG, Erlangen, Germany). Images were obtained with electrocardiography gating and during breath holding. Transaxial haste sequence covered the entire heart to study morphology and to obtain further orientation data. LV structure and function were imaged by standardized MRI protocol.[4] True fast imaging with steady-state precession cine series were obtained at the vertical and horizontal long axis for scout to line up short-axis images. The stack of short-axis images was obtained from the mitral valve plane through the apex. Slice thickness was 8 mm with a 2-mm gap, and temporal resolution was 28 to 40 msec.

To detect the myocardial scar, late gadolinium enhancement (LGE) was imaged with a 2 dimensional segmented inversion recovery gradient echo sequence 12 to 20 minutes after an injection of Dotarem (279.3 mg/ml; dose 0.2 mmol/kg). LGE images were obtained at the same views and slice/gap thickness as cine imaging.