Cardiac bone marrow cell injection for chronic ischemic heart disease

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Chapter 3

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Feasibility of Trans-Endocardial Cell Transplantation in Chronic Ischemia

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Abstract

Introduction: The aim of this study was to assess the feasibility, safety and clinical effects of trans-endocardial transplantation of autologous bone marrow-derived mononuclear cells in patients with myocardial ischemia.

Methods: In 15 patients (12 men, 67±7 years) with drug-refractory angina and myocardial ischemia on technetium-99m tetrofosmin gated single photon emission computed tomography (SPECT), bone marrow-derived mononuclear cells were injected trans-endocardially with the NOGA system (Biosense-Webster, Waterloo, Belgium). Anginal symptoms were evaluated at 3 and 6 months follow-up. At 3 months follow-up left ventricular function and myocardial perfusion were reassessed by gated SPECT.

Results: Autologous bone marrow-derived mononuclear cell transplantation was safe: laboratory measures did not reveal infarction and echocardiography showed no pericardial effusion. Arrhythmias were not observed during hospitalization, nor on repetitive Holter monitoring. Canadian Cardiovascular Society score improved in 13 of 15 patients. SPECT revealed an increased left ventricular ejection fraction (from 50±13% to 58±15% at 3 months; $P<0.01$) and an improved mean segmental regional wall motion (from 6.35±1.87 mm to 7.19±2.1 mm; $P=0.02$). The proportion of myocardial segments with normal stress-perfusion increased from 61% at baseline to 81% at 3 months follow-up ($P<0.01$). Rest-perfusion remained unchanged.

Conclusions: Trans-endocardial transplantation of autologous bone marrow-derived mononuclear cells in patients with chronic ischemia is safe, feasible and appears to contribute to relief of anginal symptoms and improvement of myocardial function and perfusion.

Introduction

Cell transplantation is currently being explored as a novel therapeutic option for patients with chronic myocardial ischemia. The main goal of bone marrow cell transplantation is to augment blood flow in ischemic myocardium through induction of angiogenesis. Improved collateral perfusion and enhanced left ventricular function have already been documented in animal models with chronic myocardial ischemia.[1] Until now, most clinical studies were carried out in patients with acute myocardial infarction. Only 2 studies containing ≤10 patients assessed the safety and feasibility of autologous bone marrow cell transplantation in patients with angina and ischemia.[2,3] Further studies are needed to confirm the safety, feasibility and effectiveness reported in these pilot trials.

The present phase I/II study tested the feasibility, safety and clinical effects of trans-endocardial transplantation of autologous bone marrow-derived mononuclear cells in patients with drug-refractory angina and myocardial ischemia. Moreover, we aimed to determine whether cell transplantation is associated with improved myocardial function and perfusion by means of technetium-99m tetrofosmin gated single photon emission computed tomography (SPECT).

Methods

Patients with ischemia on technetium-99m tetrofosmin SPECT and Canadian Cardiovascular Society (CCS) class III or IV angina pectoris (despite maximal tolerated medical therapy) without options for conventional revascularization were included in the study. An independent expert panel that reviewed the angiograms determined the ineligibility for surgical or percutaneous revascularisation. Seventeen patients fulfilled the inclusion criteria and were considered for inclusion. Exclusion criteria were: acute myocardial infarction <6 months before enrolment, history of malignancy, renal dysfunction, or unexplained haematological or biochemical abnormalities. The institutional ethics committee approved the protocol, and all patients gave informed consent.

At baseline CCS class was graded by an independent investigator. An exercise bicycle test and 24-hour Holter monitoring were performed to evaluate exercise capacity and the occurrence of arrhythmias. Technetium-99m tetrofosmin gated SPECT was carried out to assess left ventricular function and myocardial perfusion.

Bone marrow was harvested from the iliac crest under local anaesthesia, on the morning of the transplantation procedure. Mononuclear cells were isolated by Ficoll density gradient. Trans-endocardial cell injections were targeted at myocardial regions with stress-inducible ischemia (on SPECT) and injected with the NOGA system (Biosense-Webster, Waterloo, Belgium). After the procedure, heart rhythm monitoring was started and laboratory markers of myocardial necrosis were collected. Patients continued their routine drug intake after cell transplantation. Before discharge, 2-D echocardiography was performed to exclude post-procedural pericardial effusion.

At 3 and 6 months follow-up, CCS class, exercise capacity (bicycle test) and the occurrence of arrhythmia (24-hour Holter) were assessed. Gated SPECT reassessed left ventricular function and myocardial perfusion at 3 months.

For SPECT imaging, a two-day stress-rest protocol was used. The stress protocol included a bicycle exercise test or 0.14 mg/kg/minute adenosine infusion (6 minutes) in patients unable to exercise (n=7). At 1 minute before termination of the test, 500 MBq technetium-99m tetrofosmin was injected intravenously. On the second day, electrocardiography-gated resting images were obtained using 500 MBq technetium-99m tetrofosmin. Imaging was carried out with a triple-head SPECT camera system (GCA 9300/HG, Toshiba Corp., Tokyo, Japan). Reconstruction yielded standard short- and long-axis projections perpendicular to the heart-axis, which were adjusted for peak myocardial activity (100%). SPECT at 3 months was performed under identical conditions as at baseline. Two experienced observers blinded to all clinical data reviewed the SPECT images. Perfusion was assessed using segmental tracer activity (17-segment model) and expressed as percentage of maximum. Perfusion defects on stress images were considered present when tracer activity was <75%. When significant fill-in (>10%) of perfusion defects was observed on the resting images, segments were classified as ischemic. Left ventricular ejection fraction and regional wall motion were calculated using QGS software (Cedars-Sinai Medical Center, Los Angeles, California).[4]

Results are presented as mean±SD. Data were compared using paired Student's t-test or Chi-square analysis when appropriate. A P-value <0.05 was considered significant.

Results

Fifteen patients (12 men, 67±7 years) received cell transplantation. Patients' medications included nitrates (15/15), β-blockers (15/15) and calcium channel blockers (12/15). Ten patients had a previous myocardial infarction (4 anterior, 1 lateral, 5 inferior). Conventional revascularization was ineligible due to diffuse coronary artery disease with poor target vessels. Medication remained unchanged during the study period.

Patients were successfully injected with $92\pm42 \times 10^6$ mononuclear cells (10.5±2.0 injections). Sustained ventricular tachycardia was not observed during left ventricular mapping, cell transplantation or hospitalisation. Laboratory values did not reveal infarction: pre-procedural creatinine kinase was similar to in-hospital peak creatinine kinase (103±63 U/L vs. 128±66 U/L; P=NS) and in-hospital peak troponin T ranged from 0.07-0.61 µg/L (cut-off value for infarction >0.8 µg/L). 2-D echocardiography excluded post-procedural pericardial effusion. Repetitive 24-hour Holter recordings did not reveal sustained ventricular tachycardia. During the 6 months follow-up period, no significant adverse events occurred.

At 3 months, CCS class improved in 13 of 15 patients: 4 patients showed an improvement of 2 CCS classes and 9 patients improved by 1 CCS class. Three patients exhibited additional

improvement in CCS class at 6 months, whereas 4 patients showed initial improvement at 3 months followed by worsening at 6 months.

Although exercise capacity remained unchanged (100±30 Watt vs. 105±27 Watt at 3 months vs. 106±28 Watt at 6 months; both P=NS vs. baseline), the number of patients who stopped the test owing to angina decreased from 12 to 6 at 3 months (P=0.03) and 5 at 6 months out of a total of 15 patients (P<0.01). In addition, time to onset of significant ST-segment changes increased from 4.8±3.1 to 5.6±3.3 minutes at 3 months (P=0.04) and 5.8±2.7 minutes at 6 months (P<0.01).

Left ventricular ejection fraction increased from 50±13% to 58±15% at 3 months follow-up (P<0.01). In particular, left ventricular ejection fraction improved ≥5% in 11 of 15 patients (**Figure 1**). Mean segmental wall motion improved from 6.35±1.87 mm to 7.19±2.1 mm at 3 months (P=0.02).

Of the 255 segments assessed, 83 (33%) showed ischemia at baseline as compared with 30 (12%) at 3 months follow-up (P<0.01). Cell transplantation, in particular, improved stress perfusion, whereas resting perfusion remained unchanged. The proportion of segments with ≥75% tracer uptake (normal perfusion) during stress increased from 156 of 255 (61%) at baseline to 206 of 255 (81%) at 3 months (P<0.01), whereas the proportion of segments with ≥75% tracer uptake at rest remained unchanged (227 of 255 (89%) vs. 234 of 255 (92%); P=NS).

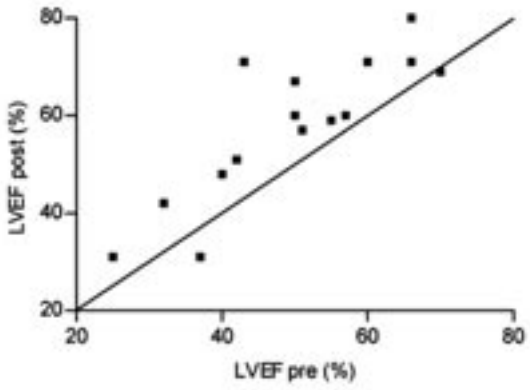

Figure 1
Scatter plot showing individual left ventricular ejection fractions (LVEF) before (pre) and 3 months after cell transplantation (post). The solid line represents the line of identity.

Discussion

The present phase I/II study in patients with severe angina and myocardial ischemia, who were trans-endocardially transplanted with autologous bone marrow-derived mononuclear cells, showed excellent safety and feasibility results. The procedure was well-tolerated and no procedure-related side effects occurred. No major adverse event occurred during the 6 months follow-up period. Furthermore, major clinical improvements were observed: anginal symptoms reduced, left ventricular function increased and myocardial perfusion augmented.

As the current study comprises no control group, the observed changes cannot be unambiguously attributed to bone marrow cell transplantation. Other contributing factors might be placebo effect, spontaneous improvement and medical treatment. However, it is rather rare that left ventricular function and myocardial perfusion improve without intervention, and cardiovascular drugs remained unchanged in all patients. The follow-up period of 6 months can be considered a limiting factor: the long-term effects of cell transplantation remain to be determined. Additional randomized, placebo-controlled studies are warranted to further pursue the strategy of cell transplantation in patients with angina and chronic ischemia.

References

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