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Restitution of the Infarcted Myocardium- the Role of Stem Cells

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Even after optimal reperfusion strategies implementing percutaneous coronary intervention (PCI) with stent implantation and modern medical regimen for patients with acute myocardial infarction, myocardial salvage is often incomplete and adverse ventricular remodeling with subsequent heart failure develops.

The transplantation of autologous bone marrow stem cells (BM-SCs) via the intracoronary delivery route after PCI of the infarct related artery (IRA) has been investigated in several observational studies which proved the safety and feasibility of the method.[1] The results of the randomized studies were rather controversial. The BOOST study (Bone Marrow transfer to enhance ST-elevation infarction regeneration) was the first randomized study with patients receiving either bone-marrow derived mononuclear cells or placebo 5 days after primary PCI. The improvement of the ejection fraction reported in the cell infusion group at 6 months was attenuated during a follow-up study of 18 months. Of note, a similar restenosis rate (13%) was reported between the 2 groups.[2]

In the larger double-blind study (Reinfusion of Enriched progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction, REPAIR-AMI), 204 patients were randomized in 2 groups, one receiving bone-marrow derived mononuclear cells intracoronarilly and the other receiving placebo infusion.[3,4] At 4 months, left ventricular ejection fraction improved significantly in the cell treated group. This group also showed greater clinical benefit during a follow-up of 12 months regarding death, myocardial infarction, revascularization and re-hospitalization for heart failure.

In a recent study from Lunde et al[5] (Autologous Stem-Cell Transplantation in acute Myocardial Infarction, ASTAMI), patients were randomized to either intracononary cell infusion or placebo 6 days after primary PCI for anterior myocardial infarction. Six months later echocardiography, SPECT and MRI revealed no difference in left ventricular volumes, ejection fraction or infarct size between the 2 groups.

Janssens et al[6] randomized patients early after acute myocardial infarction (within the first 24 hours) into intracoronary cell delivery or placebo. The cell treated group showed an improvement in perfusion and regional contractility, but no difference was noted in the increase of the global ejection fraction between the 2 groups.

Based on the knowledge that bone marrow-derived progenitor cells can reach the target organ through peripheral blood and that tissue repair is mediated by cytokines secreted from sites of ischemic injury an effort was made to evaluate the enhancement of this natural repair mechanism by exogenous delivery of G-CSF (Granulocyte-colony-stimulating-factor) and/or other cytokines on cardiac repair.[7]

In the MAGIC trial (Myocardial Regeneration and Angiogenesis in Myocardial Infarction With G-CSF and Intracoronary Stem Cell Infusion)[8], Kang et al delivered

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G-CSF subcutaneously starting 4 days before PCI for patients with acute and remote myocardial infarction. Even though there was a favorable effect of the mobilization of the stem/progenitor cells on the improvement of left ventricular ejection fraction and regional perfusion, the study was terminated prematurely because of the high incidence of increased restenosis rate in the group treated with G-CSF. The intracoronary transplantation of G-CSF mobilized peripheral blood stem cells vs an untreated control group was studied in the subsequent MAGIC Cell-3-DES study[9]. Two patient groups were studied after being treated with PCI and drug eluting stents after myocardial infarction. This study showed an improvement in left ventricular dimensions and ejection fraction, but most importantly no increased restenosis rate was noted.

In the FIRSTLINE-AMI[10,11] study from Ince et al, 25 patients received G-CSF approximately 90 minutes after primary PCI for acute myocardial infarction. The cardiac function (regional and global ejection fraction, left ventricular dimensions and viability) increased significantly in the G-CSF group compared to the control group and there were no adverse events noted, including restenosis.

The recent study REVIVAL-2[12] by Zohlnhofer was a double-blind study with 114 patients, who were randomized to subcutaneous delivery of G-CSF for 5 days after primary PCI or placebo. At 4-6 months there was no difference in the reduction of the infarct size and improvement of the left ventricular ejection fraction between the 2 groups.

In conclusion, even though the exact mechanism of cell transplantation still remains unclear, small observational clinical studies have shown the feasibility and safety of the method in patients treated with primary PCI and stent implantation of the IRA after acute myocardial infarction. The results of the recent randomized clinical trials were rather controversial regarding the effects of the intracoronarilly delivered bone marrow-derived stem cells or G-CSF mobilized bone marrow stem/progenitor cells on cardiac performance, dimensions and perfusion of the infarcted area. Further large, double-randomized, controlled trials are needed in order to establish the efficacy and possible role of cell therapy in the management patients in the early post-infarction period.

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