Stem Cell Therapy

A Holistic Approach?

By Heidi Fritz ND

Autologous stem cell therapy involves expansion and transplantation of a stem cell clone or line into the same individual from whom the cell line was originally isolated from, with the intention of treating a specific condition. A growing body of research has uncovered promising results for autologous stem cell therapy in a variety of cardiovascular conditions, in particular the treatment of acute myocardial infarction (AMI). It appears that stem cell therapy may enhance myocardial repair post AMI, and may increase left ventricular function when used in conjunction with other firstline therapies such as percutaneous coronary intervention (PCI, e.g., angioplasty or coronary artery bypass). This article reviews the rationale, clinical applications, and current research with respect to autologous stem cell therapy for AMI.

Derivation of Stem Cells

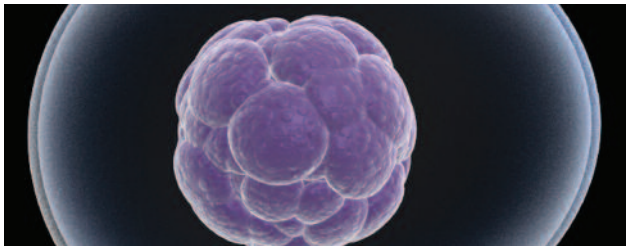
Autologous stem cell transfer, which involves cells being taken from and given back to the same individual, differs from allogenic transplantation of stem cells in which cells from one individual are transferred to another individual, as occurs with use of embryologic stem cells. Autologous adult stem cell therapy is therefore both ethically viable and ideally immunologically matched, eliminating risk of immune rejection of the transplanted cells.

Adult stem cells may be derived from a variety of tissue sources, including bone marrow, circulating blood cells and skeletal muscle cells. Of these unselected bone marrow (BM) mononuclear cells, selected CD34+ cells, BM-derived mesenchymal stem cells, and circulating progenitor cells are being used in human clinical trials for cardiovascular applications (Charwat 2008).

As the above indicate, even within a specific "tissue derived" type of stem cell, for instance bone marrow stem cells, there lie several subsets of cell lines expressing different surface receptors (eg., CD34+). The implications of this for therapy is only now beginning to be explored further, with findings in the TOPCARE-AMI trial that "greater LVEF improvement [was] associated with good migratory capacity of progenitor cells, evidenced as the chemotaxis to stromal cell-derived factor (SDF-1)" (Tendera 2005). This suggests that the chemotactic capacity of specific cell subtypes may be of importance in mediating therapeutic effects. The problem of what subset(s) offers most clinical benefit, however, is yet to be answered.

Cardiovascular Applications and Mechanism of Action

The cardiovascular applications of autologous stem cell therapy currently under investigation range from AMI and ischemic heart disease to congestive heart failure (CHF) and stroke. Proposed mechanisms of action for benefit on AMI target enhancement of myocardial salvage and regeneration via; 1) therapeutic angiogenesis improving the blood supply to the infarct border zone; 2) paracrine modulation of myocardial fibrosis and remodelling; and 3) transdifferentiation of progenitor cells into functional cardiomyocytes (Tendera 2005).



Animal studies using CD34+ bone marrow stem cells reinforce these proposed effects: in infracted animals, cells were found to infiltrate damaged myocardium preferentially, and resulted in increased microvascularity and decreased matrix deposition and fibrosis (Charwat 2008). Combined, these mechanisms result in improved left ventricular function as measured by increased left ventricular ejection fraction (LVEF) and decreased left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV), confirmed by measurement in clinical trials.

Summary of the Evidence: RCT's

Large randomized controlled trials have demonstrated positive effects of stem cells therapy on regional and global left ventricular function (see Table 1) on page 65.

Meluzin (2008) conducted a 12-month randomized controlled trial of intracoronary autologous bone marrow cells in 60 patients with AMI to determine long-term effects of this therapy. Treatment consisted of one time injection of 10^7 or 10^8 cells. End point measures were global and regional left ventricular function as reflected by Doppler and SPECT imaging at baseline, three, six, and 12 months. While early results indicated greater improvement in regional left ventricular function in favour of the high dose regimen, these differences disappeared by 12 months. Global left ventricular ejection fraction (LVEF) increase by 6%, 7%, and 7% at three, six, and 12 months respectively, which was a significant improvement over that of the control group. Authors suggested that although initial *regional* improvements may decline in the long-term, significant improvements in *global* function persist.

Schachinger (2006) (REPAIR-AMI trial) conducted a relatively large multicenter controlled trial involving 204 patients post AMI. Subjects were given either intracoronary infusion of progenitor cells derived from bone marrow (BMC) or placebo medium into the infarct artery three to seven days after successful reperfusion therapy. The endpoint measure was left ventricular function. At months' follow-up, the absolute improvement in the global LVEF was significantly greater in the BMC group than in the placebo group (5.5% vs. 3.0%). At one year, intracoronary infusion of BMC was significantly associated with a reduction in combined clinical end point of death, recurrence of myocardial infarction, and any revascularization procedure. Authors determined that patients with lower function at baseline (LVEF at or below the median value of 48.9%) derived the most benefit as measured by absolute improvement in LVEF, which was 5.0% for this subgroup.

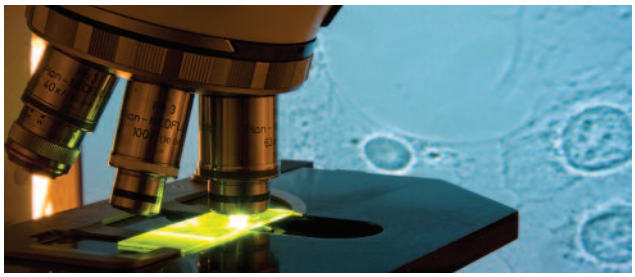
Gyöngyösi 2009 (MYSTAR trial) studied the effect of administering bone marrow derived stem cell therapy at two different time points. From a total of 60 patients, one group received stem cell therapy at three-six weeks post AMI whereas the second group received stem cell therapy at three-four months post AMI. Both groups received cells by combination of two routes, intracoronary and intramyocardial. Dose of cells delivered was 200 x 10^6 (early group) and 194.8 x 10^6 (late group) stem cells intramyocardially, and 1.30 x 10^9 (early) and 1.29 x 10^9 (late) cells intra-artery. At three months, mean changes in infarct size were -3.5% in the early group and -3.9% in the late group; changes in ejection fraction were 3.5% and 3.4% respectively. At nine-12 months, the mean changes in global ejection fraction (LVEF) were 4.3% in the early group and 4.0% in the late group, a nonsignificant difference between groups, but a significant improvement from baseline. This improvement at nine-12 months does not favour a particular time point for intervention, however it confirms a long-lasting effect from (combined) bone-marrow-derived mononuclear therapy. Other multiple trials have demonstrated similar benefits on left ventricular function. See Table 1 on page 65 for listing and summary.

Meta-Analyses and Systematic Reviews

Martin-Rendon (2008) reviewed the safety and efficacy of autologous bone marrow-derived stem cells transplantation in acute myocardial infarction (AMI), selecting 13 trials (811 participants) for inclusion. Stem cell therapy was found to improve left ventricular ejection fraction (LVEF) by 2.99% (95% CI), significantly reduce left ventricular end-diastolic volume (LVEDV) by 4.74 ml (95% CI), and reduce myocardial lesion area by 3.51% (95% CI) compared to controls. Significant improvement in LEVF was furthermore favoured when cells were infused within seven days post AMI, and by BMSC dose higher than 10^8. Non-significant trends were observed in favour of benefit for most clinical outcomes examined, such as mortality, morbidity (reinfarction, arrhythmias, restenosis, revascularization), adverse events, quality of life and requirement for re-operation.

Table 1: Autologous Bone Marrow Derived Stem Cells for AMI: RCT's

Description	Outcomes	Reference
60 patients with left ventricular ejection fraction (LVEF) <45% after AMI were randomly assigned stem cell delivery via intramyocardial injection and intracoronary infusion at either 3-6 weeks or at 3-4 months post AMI.	Mean changes in infarct size at 3 months were -3.5% in the early group and -3.9% in the late group; changes in ejection fraction were 3.5% and 3.4%, respectively. Combined cardiac stem cell delivery was found to induce a moderate but significant improvement in myocardial infarct size and left ventricular function.	Gyöngyösi 2009 (MYSTAR)
12-month RCT of intracoronary autologous bone marrow cells in 60 patients with AMI to determine long-term effects of this therapy. End point measures were global and regional LV function as reflected by Doppler and SPECT imaging at baseline, 3, 6, and 12 months.	Treatment with autologous BMC's results in sustained benefit to global left ventricular systolic function, although some of the benefit on regional systolic function of the infracted wall was partially lost over the 12 month follow-up period.	Meluzin 2008
Multicenter RCT of 204 patients with AMI given either intracoronary infusion of progenitor cells derived from bone marrow (BMC) or placebo medium into the infarct artery 3 to 7 days after successful reperfusion therapy. Endpoint measure was left ventricular function.	At 4 months, the absolute improvement in the global LVEF was significantly greater in the BMC group than in the placebo group (5.5% vs. 3.0%). Patients with a baseline LVEF at or below the median value of 48.9% derived the most benefit (absolute improvement in LVEF, 5.0%). At 1 year, intracoronary infusion of BMC was associated with a reduction in combined clinical end point of death, recurrence of MI, and any revascularization procedure.	Schachinger 2006 (REPAIR-AMI)
RCT investigating use of intracoronary autologous bone marrow cell transplantation for treatment of AMI in 20 patients. Endpoints were LVEF, left ventricular end diastolic internal diameter (LVDd) and myocardial perfusion defect scores as measured by echo and SPECT at 1 and 6 weeks post AMI.	From weeks 1 to 6, LVEF increased from 53.8% to 58.6% in the BMC group, but did not change in the controls group. LVDd was unchanged in the BMC group but increased from 50.4 to 55.2mm in the controls. Myocardial perfusion defect scores decreased from 21 to 13 in the BMC group but did not change in the control group.	Ge 2006 (TCT-STAMI)
RCT involving 20 patients with ACMI and anterior descending artery occlusion on angiography. LV segmental function post AMI assessed by Doppler and strain imaging 6 months after intervention. Endpoints were LVEF, end diastolic volume (EDV), and end systolic volume (ESV).	At 6 months, LVEF in the BMC group was higher than that in the controls, at 59.33% versus 50.30% respectively, though there had been no difference at baseline. Similarly, EDV and ESV were greater in the control group versus BMC group at 6 months: EDV 154.89 vs 104.85ml; ESV 82.91 vs 49.54ml).	Ruan 2005
RCT to investigate the effectiveness of intracoronary injection of bone marrow mesenchymal stem cells (BMSC's) in patients with AMI. 69 patients with AMI and having had PCI intervention were assigned to BMSC or saline (control) groups. Endpoint was left ventricular function at 6 months.	The proportion of subjects with function defect decreased significantly in the BMSC group vs controls at 3 months. LVEF at 3 months increased significantly in the treatment group, 67%, versus 49% in controls. Left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV) both decreased significantly in the treatment group compared to controls.	Chen 2004
Global LVEF at 6 months increased by 0.7 percentage points in the controls and 6.7 percentage points in the BMC group. Cell transfer did not increase the risk of adverse clinical events, in-stent restenosis, or arrhythmias.	60 patients were assigned to BMC transfer 4.8 days after PCI for AMI or a control group receiving standard medical treatment only. Endpoint was 6 month change in LVEF.	Wollert 2004 (BOOST)



Zhang (2008) conducted a systematic review of intracoronary BMSC transfer after coronary reperfusion therapy for primary AMI, with five trials and 620 patients included. The combined endpoint of death, recurrence of myocardial infarction, revascularization procedures, or rehospitalization for heart failure was significantly reduced in the BMSC group compared with the control group at more than one year follow-up (OR = 0.45, 95%CI). Occurrence of revascularization and the combined endpoint death, recurrence of myocardial infarction, or revascularization procedures were also significantly reduced when BMSC transplantation was performed between four and seven days after primary percutaneous coronary intervention (PCI) (OR=0.60, 95%CI, OR=0.58 95% CI respectively).

Abdel-Latif (2007) conducted a review of the safety and efficacy of adult bone marrow stem cell transplantation for ischemic heart disease, including acute myocardial infarction and chronic forms of ischemic heart disease. A total of 18 RCT's and cohort studies (999 patients) were included. Bone marrow stem cell transplantation was found to improve LVEF 3.66% (95% CI), reduce infarct scar size 5.49% (95% CI), and reduce left ventricular end-systolic volume (LVESV) 4.80 ml (95% CI).

Clinical Considerations

Although the numbers cited above, ranging from 2-4% increase in LVEF, may seem relatively low, they nonetheless parallel results obtained by previous studies combining thrombolytic therapy with PCI for AMI (CADILLAC and ADMIRAL trials), in which average improvement in LVEF was 2.8% and 4.1%, respectively (Martin-Rendon 2008). It has therefore been suggested that the moderate improvements resulting from autologous stem cell therapy may translate into significant clinical benefit (Martin-Rendon 2008). Overall, autologous stem cell therapy has a high safety profile, and no increased occurrence of any serious adverse events has been found. It would appear that the invasiveness of the injection procedure itself represents the greatest degree of risk involved.

Conclusion

Taken together, the results of these studies suggest a modest but significant degree of clinical benefit to be obtained from complementary use of autologous stem cells in conjunction with standard medical treatment and percutaneous coronary interventions. Autologous bone-marrow derived stem cell therapy has been found to improve left systolic function as reflected by increased LVEF ranging from 2-4% in meta-analyses; left ventricular end-diastolic volume (LVEDV) decreased by 4.74 ml; and myocardial lesion area decreased by 3.51%. Future directions of research include determinations of optimal dose and dosing schedule; route of delivery; identification of most effective cell types/subtypes; identification of the patient subset most likely to benefit from therapy; and the development of standardized procedures for isolating these cell subtypes. ■

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