FOLIA HISTOCHEMICA ET CYTOBIOLOGICA
Vol. 43, No. 4, 2005
pp. 233-235

Review article

Clinical trials using autologous bone marrow and peripheral blood-derived progenitor cells in patients with acute myocardial infarction

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Abstract: This paper discusses the current data concerning the results of major clinical trials using bone marrow-derived and peripheral blood-derived stem/progenitor cells in treatment of patients with acute myocardial infarction (AMI) and depressed left ventricular ejection fraction. In all major trials (TOPCARE-AMI, BOOST), the primary outcome measure was increase in left ventricular systolic function (LVEF) and left ventricle remodeling. The most consistent finding is the significant increase in LVEF. Some trials suggest also reduction of left ventricular remodeling. Although the absolute LVEF increase is small (6-9%), it may substantially contribute to the improvement of global LV contractility. None of the studies in AMI patients treated with intracoronary infusion of progenitor cells revealed excess risk of arrythmia, restenosis or other adverse effects attributable to the therapy. The exact mechanism of improved myocardial contractile function remains unknown, however, there are several possible explanations: therapeutic angiogenesis improving the blood supply to the infarct border zone, paracrine modulation of myocardial fibrosis and remodeling (*e.g.* inhibition of myocyte apoptosis) and transdifferentiation of stem/progenitor cells into functional cardiomyocytes. No study showed the superiority of the particular subpopulation of autologous progenitor cells in terms of left ventricular function improvement in AMI. In fact, most of the clinical trials used the whole population of mononuclear bone marrow-derived progenitor cells, peripheral blood derived progenitor cells (endothelial progenitors).

Key words: Progenitor cells - Bone marrow - Peripheral blood - Acute myocardial infarction

Introduction

In spite of the widespread availability of percutaneous coronary intervention (PCI) and pharmacological reperfusion therapy in patients with acute myocardial infarction (AMI), the long-term outcomes in substantial group of patients is unfavorable due to large area of myocardial necrosis with subsequent contractile dysfunction leading to development of ischemic cardiomyopathy and heart failure. It was shown in animal models that bone marrow-derived and peripheral blood-derived adult progenitor cells have the potential to improve myocardial recovery in ST-segment elevation myocardial infarction (STEMI) [2, 4, 8]. Moreover, clinical trials were carried out to test the hypothesis that bone marrow-derived progenitor cells may improve the myocardial recovery after AMI.

Mechanisms of myocardial repair

The exact mechanism of improved myocardial contractile function remains unknown. The following phenomena can contribute to myocardial salvage after therapy with progenitor cells [2, 4, 8]: (1) therapeutic angiogenesis improving the blood supply to the infarct border zone (2) paracrine modulation of myocardial fibrosis and remodeling (*e.g.* inhibition of myocyte apoptosis) and (3) transdifferentiation of progenitor cells into functional cardiomyocytes (the most questionable pathway).

Types of adult progenitor cells used in clinical trials

So far no study has shown the superiority of any particular subpopulation of autologous progenitor cells in terms

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Lecture presented at the Third Annual Meeting of the European Stem Cell Therapeutics Excellence Centre, October 6-9, 2005, Cracow, Poland

Table 1. Major clinical trials involving intracoronary infusion of bone marrow-derived or peripheral blood-derived stem cells in acute myocardial infarction

Study	Type/source of cells	N	Follow-up	Outcome measures
Strauer *et al.* [7]	Intracoronary BMC	10	3 months	↔ LVEF (LV angio) ↓ LVESD ↑ myocardial perfusion ↑ regional contractility
TOPCARE-AMI [5]	Intracoronary BMC or CPC	59	1 year	↑ LVEF (MRI) ↔ LVEDV ↓LVESV ↑ viability ↑ flow reserve
BOOST Trial [9]	Intracoronary BMC	60	6 months	↑ LVEF (MRI) ↔ LVESV, LVEDV
Fernandez-Aviles *et al.* [3]	Intracoronary BMC	20	6 months	↑ LVEF (MRI) ↓LVESV ↔ LVEDV

BMC - bone marrow-derived cells; CPC - circulating progenitor cells; LVEF - left ventricular ejection fraction, LVEDV - left ventricular end-diastolic volume, LVESV - left ventricular end-systolic volume, LVESD - left ventricular end-systolic diameter, MRI - magnetic resonance imaging

Table 2. Safety of intracoronary infusion of progenitor cells in acute myocardial infarction in major clinical trials.

Study	Type of adverse event	N	Relation to therapy	Outcome
Strauer *et al.* [7]	(-)	10	(-)	(-)
TOPCARE-AMI [5]	Thrombotic occlusion of IRA during second angiography prior to cell infusion	1	Instrumentation-related	Recovered
	AMI (stent thrombosis in vessel other than IRA in index AMI)	1	None	Recovered
	Fatal AMI (subacute stent thrombosis in IRA)	1	Unlikely	Died
BOOST Trial [9]	NSTEMI (vessel other than IRA in index AMI)	1	None	Recovered
	Hospitalization due to worsening of heart failure	1	None	Recovered
	VT/VF inducible in EPS	2	None	Recovered
Fernandez-Aviles *et al.* [3]	TIA	1	None	Recovered

IRA - infarct-related artery; TIA - transient ischemic attack, VT - ventricular tachycardia; VF - ventricular fibrillation, AMI - acute myocardial infarction; NSTEMI - non-ST-segment elevation acute myocardial infarction.

of left ventricular function improvement in AMI. In fact, most of the clinical trials used the whole population of mononuclear bone marrow-derived progenitor cells, peripheral blood derived progenitor cells (endothelial progenitors). Skeletal muscle myoblasts used in chronic heart failure are not feasible in STEMI patients because the need of expansion in cultures lasting days or weeks [2, 9]. TOPCARE-AMI investigators reported greater LVEF improvement associated with good migratory capacity of progenitor cells evidenced as the chemotaxis to stromal cell-derived factor (SDF-1) suggesting that cells positive for SDF-1 receptor CXCR4 may be important in cardiac salvage [1]. This issue will be addressed in REGENT multicenter trial which compares two population of cells - unselected bone marrow-derived mononuclear cells with sorted CD34/CXCR4+ cells - in patients with AMI and low LVEF.

Outcome measures

In all completed trials, the primary outcome measures are the parameters of left ventricular systolic function (LVEF) and remodeling - changes in left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular end-systolic diameter LVESD) measured by the most sensitive diagnostic method - cardiac magnetic resonance imaging (MRI), as well as contrast ventriculography and

echocardiography. Some studies employed MRI-assisted functional tests (coronary flow reserve) and assessment of infarct size and mass (TOPCARE-AMI) [5, 9]. The most consistent finding is the increase in LVEF (Table 1). Some trials suggest also reduction of left ventricular remodeling (TOPCARE-AMI). Although the absolute LVEF increase is small (6-9%), it may substantially contribute to the improvement of global LV contractility. Also longer follow-up seems necessary since as shown in TOPCARE-AMI there is further improvement in LVEF as revealed by MRI performed after 4 months and after 1 year [5].

Safety

As in every other experimental therapy, the safety issues remain fundamental. Previous data concerning the proarrythmogenic properties of skeletal muscle myoblasts [6] warranted ECG Holter monitoring in every patient receiving progenitor cells. Some trials also used invasive electrophysiological study [9]. So far none of the studies in AMI patients treated with intracoronary infusion of progenitor cells revealed excess risk of arrythmia, restenosis or other adverse effects attributable to the therapy (Table 2). The overall rate of cardiovascular adverse events did not differ between the patients treated routinely and subjects receiving the progenitor cell infusion [3, 5, 9].

Which patients benefit most?

Most of the trials involved small groups of patients, so the validity of sub-group analyses is questionable. It seems that the benefits of cell therapy are uniformly distributed regardless of sex, age, renal function, presence of hypertension, hyperlipidemia, diabetes, extent of coronary atherosclerosis and time to revascularization. No associations were also found between the cell type and number and LVEF increase [1, 5, 9]. However, baseline LVEF value was an independent predictor of LVEF improvement, suggesting that patients with the most substantial myocardial damage have the most significant improvement after cell therapy [5].

The efficiency of the progenitor cell therapy will be assessed in ongoing large clinical trial REPAIR-AMI (200 patients). Based on the results of randomized clinical trials, the intracoronary infusion of progenitor cells seems to be a safe and effective adjunctive method of treatment in patients with AMI who after successful coronary reperfusion develop significant left ventricular dysfunction, however, the double-blind placebo-controlled trial is necessary to confirm the findings.

Acknowledgements: The study was supported by grant PBZ-KBN-099/P05/2003 from the Ministry of Science.

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Received: June 28, 2005
Accepted: June 30, 2005