Cell quality in the ASTAMI study

Schächinger et al. recently reported clinical improvement after treatment of acute myocardial infarction with intracoronary injection of autologous bone-marrow-derived mononuclear cells (MNCs) (the REPAIR-AMI Trial). Here, the authors discuss whether lack of improvement in global left ventricular function in our study, the ASTAMI study; could be related to impaired cell quality or insufficient cell numbers. We believe this is unlikely for the following reasons:

(i) Comparable density gradient centrifugation techniques have been used for isolation of MNCs in the REPAIR-AMI and the ASTAMI studies. The density gradient solutions used for MNC separation, Lymphoprep™ and Ficoll-Hypaque (Ficoll-Paque™), contain ficoll and sodium diatrizoate at identical concentrations.

(ii) In the ASTAMI study, MNCs were kept at 4–8°C overnight in 0.9% NaCl and 20% autologous heparin plasma, cell concentration <10^6 cells/ml. Cold saline-plasma storage of bone marrow or peripheral blood stem cells (PBSCs) for transplantation is being used worldwide for intercontinental transportation or prior to cryopreservation in this study. To mention one of several examples: over the past 12 years, 163 multiple myeloma patients have received autologous PBSC transplantation in our hospital. PBSCs had been stored overnight at 4–8°C in saline-plasma prior to cryopreservation. Stem cell engraftment occurred in >90% of the patients within 3 weeks and for the rest within the next few weeks.

(iii) In the ASTAMI study, only MNCs with cell viability >90% were injected. The acridine orange/ethidium bromide technique was used for viability assessment; a sensitive, reliable, and reproducible method utilized for numerous viability tests, e.g. pre-transplant cell control and lymphocyte toxicity cross-match analyses.

(iv) In parallel studies, functional assays on bone marrow MNCs from healthy controls, isolated and stored as for the ASTAMI patients, were shown to be normal by their numbers of the haematopoietic progenitor cell colonies CFU-GM and BFU-E (unpublished results).

(v) The relative number of isolated MNCs in the ASTAMI study was comparable to other studies. In addition, injected cell numbers have not been shown to correlate to changes in cardiac function.

Taken together, the cell-processing protocol in the ASTAMI study produces MNCs that are viable and functional. Whether intracoronary injection of autologous bone marrow MNCs has a beneficial effect still remains to be confirmed.

References


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Improved clinical outcome after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial

We read with great interest the recent article by Schächinger et al. showing improved 1-year clinical outcomes in patients with acute myocardial infarction receiving intracoronary administration of bone marrow-derived progenitors cells (BMCs) after successful reperfusion therapy. The authors attribute the improved clinical outcomes in the treatment group to the recovery of global left ventricular contractile function within 4 months, as recently reported in the same patient population.7 However, we believe that factors other than administration of BMCs may have influenced left ventricular ejection fraction (LVEF) recovery and, hence, clinical outcomes in their study. First, we can suppose that spontaneous LVEF recovery was already occurring in both groups before BMCs or placebo administration. Indeed, baseline LVEF was 46.7±10 and 47.5±10% in controls and BMC-treated patients, respectively—values higher than that used as a threshold for patient inclusion in the study (<45%). This spontaneous recovery may be explained by the mean delay between enrolment and baseline LVEF measurement (4.3±1.3 days). Secondly, and more importantly, two major determinants of LVEF recovery—time-to-reperfusion and infarct location—are possible confounders in this study. According to Sheiban et al.,7 LVEF recovery is usually observed after primary angioplasty if coronary flow is restored <4 h from symptom onset, whereas no significant improvement occurs afterwards. This time “window” may be even narrower in anterior infarctions. Indeed, we have observed no significant recovery in LVEF after primary angioplasty despite an average shorter time-to-reperfusion (2.5±1.4 h) when only anterior myocardial infarctions were considered.4 In the REPAIR-AMI study, however, the authors analysed anterior and inferior infarctions together, despite the fact that these two infarct locations differ in terms of acute left ventricular impairment severity, LVEF recovery and clinical outcome after reperfusion therapy.2,8 In BMC-treated patients, anterior infarctions were less represented (64 vs. 76%), which may explain the small difference in LVEF recovery between the placebo and treated groups (3.0±6.5 vs. 5.5±7.3%), and in clinical outcomes.1,2 Moreover, mean reperfusion time was >7 h, an interval usually not associated with LVEF improvement, particularly in anterior infarctions.3,4 The combination of different times to treatment and infarct locations may have a major influence on LVEF recovery.