Autologous bone marrow mononuclear stem cells for acute myocardial infarction: is it only about time?

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This editorial refers to ‘A randomized double-blind controlled study of early intracoronary autologous bone marrow cell infusion in acute myocardial infarction: the REGENERATE-AMI clinical trial’, by F. Choudry et al., on page 256.

In 2002, Strauer et al.1 reported the results of the first phase I study testing the safety of intracoronary (IC) administration of autologous bone marrow mononuclear stem cells (BMMSCs) for acute myocardial infarction (AMI). Since then, we have seen a series of trials using mixed cell types with heterogeneous designs in terms of both the number and the timing of BMMSCs administration that have yielded conflicting results2 (Figure 1). For example, Nowbar et al.3 found no beneficial effect on left ventricular ejection fraction (LVEF) when analysing BMMSCs trials without any discrepancies, while a meta-analysis by Afzal et al.4 (48 studies; 2602 patients) showed an improvement in both LVEF (+2.92%) and infarct size (−2.25%), as well as remodelling. Taken as a whole, these contradictory findings have left the general cardiology community somewhat indifferent and have arguably shrouded the field of BMMSCs research in a dark fog from which it has yet to emerge.

In this issue of the journal, Choudry et al.5 present the results of the REGENERATE-AMI trial, evaluating the effect of IC autologous BMMSCs on left ventricular (LV) function when delivered within 24 h of successful reperfusion therapy. While REGENERATE-AMI did not meet its primary endpoint, there is much potential value in trying to place this trial’s design and results in context in order hopefully to illuminate a way forward for regenerative therapy after successfully perfused AMI.

REGENERATE-AMI5 enrolled 100 patients with AMI across five European centres from 2008 to 2013, who were randomized to either IC BMMSCs or placebo within 24 h of successful percutaneous coronary intervention (PCI). The primary endpoint was the change in the LVEF at 1 year using advanced cardiac imaging. Secondary endpoints included infarct size and LV remodelling at 3, 6, and 12 months. In addition, biological and clinical heart failure (HF) parameters, quality of life scores, and 1-year major adverse cardiac event (MACE) rates were analysed. Similar to several previous trials, the authors found that injection of BMMSCs resulted in a reduction in infarct size, but without any improvement in LVEF, New York Heart Association (NYHA) class, N-terminal pro brain natriuretic peptide (NT-proBNP) levels, or the MACE rate. The trial did confirm, however, that ‘early’ BMMSCs injection was both feasible and safe.

Timing of the IC BMMSC injection

REGENERATE-AMI is unique in that the investigative team was able to harvest and deliver bone marrow aspirate successfully within a median of 10 h post-PCI. In an era of contracting healthcare funding, showing that such a procedure can be performed without extending hospital stay or resulting in costly complications is a feat in itself. However, this strength might have also been the study’s Achilles heel. It is possible that such early BMMSCs injection might limit retention, survival, and homing in the infarcted myocardium. It is well known that a ‘hostile’ myocardium exists in the first days after AMI, characterized by high coronary microcirculation resistance due to inflammation, oedema, and possibly microembolization related to either the thrombotic coronary event or the PCI procedure. Janssens et al.6 also safely performed autologous IC BMMSCs transfer within 24 h of optimal reperfusion therapy and also failed to show any improvement in global LV function recovery. There was, however, a similar reduction in infarct size. Such early BMMSCs administration is supported by a pilot study by Huang et al.7 that did not show a difference between administration within 24 h vs. 3–7 days after primary PCI with regards to LV functional recovery.

In most previous studies, however, IC BMMSCs administration was performed within the first 7 days after AMI.8 Moreover, in
the REPAIR-AMI trial, the beneficial effects of BMMSCs appeared to be most pronounced with cell administration between 5 and 7 days,
whereas Afzal et al.\(^8\) reported that injecting BMMSCs 3–10 days after AMI led to the most significant improvement in cardiac functions, but the reduction of infarct size was only seen when cells were transplanted within the first 48 h after AMI. On the other hand, the TIME trial\(^9\) compared BMMSCs therapy at 3 days vs. 7 days after AMI, and the Late TIME trial\(^10\) tested BMMSCs injection 2–3 weeks after AMI against placebo, but neither trial was able to show a beneficial effect on LV function. As such, the optimal timing of BMMSCs administration remains an open question, but, taken as a whole, the evidence would suggest that the benefit of BMMSCs for AMI may vary depending on the inflammation status of the ischaemic myocardium.

### The population

Similar to previous studies, REGENERATE-AMI included patients with significant anterior wall motion abnormality on the LV angiography performed at the index PCI procedure. While both intuitive and supported by data—a previous meta-analysis\(^11\) confirmed that cell therapy is more effective on LV function recovery in the presence of significant LV dysfunction at baseline (LVEF < 40%)—relying on such a precocious evaluation of LV function for study enrolment might have had the effect of selecting a population of patients with a low likelihood of needing BMMSCs in the first place, as LV dysfunction may well have been overestimated due to stunning that typically recovers well after timely reperfusion therapy. Moreover, very rapid provision of primary PCI, while representing the very best of modern AMI care, probably helped to ensure a population at low overall risk. A low HF risk population could well explain neutral results in terms of LVEF and HF endpoints, despite a statistical reduction in infarct size.

### Bone marrow stem cells: type, dosage, and harvesting methods

Bone marrow cells isolated by density gradient centrifugation comprise a mixture of cells that could have differential effects on myocardial recovery. Unfractionated BMMSCs contain monocytes, lymphocytes, haematopoietic progenitor and precursor cells, and occasional haematopoietic stem cells.

Injection of selected BMMSCs can be considered in order to optimize stem cell effects on myocardial transdifferentiation, neovascularization, and inhibition of apoptosis, such as CD133\(^+$\) cells. In a phase I study, Bartunek et al.\(^12\) showed that IC administration of enriched CD133\(^+$\) cells was associated with improved LV performance, increased myocardial perfusion, and enhanced viability. However, a high rate of coronary events was reported in the CD133\(^+$\) group, explained by a higher rate of in-stent bare metal stent restenosis and luminal loss of the infarct-related artery. In the phase II COMPARE-AMI trial,\(^13\) we demonstrated that IC administration of 10\(^6\) CD133\(^+$\) cells was safe at 4 months of follow-up and did not contribute to any acceleration of atherosclerosis or a higher rate of drug-eluting stent restenosis as compared with placebo.\(^14\)

The effect of CD133\(^+$\) on the LVEF as assessed by magnetic resonance imaging (MRI) is to be presented in the near future.

The optimal dosage of BMMSCs is not yet known. In REGENERATE-AMI, an average of 59.8 × 10\(^6\) mixed BMMSCs were delivered. While Clifford et al.\(^15\) showed a positive correlation between a cell number > 10\(^9\) and improvements in infarct size and LVEF, other investigators failed to show a dose-dependent effect.\(^11\)

Moreover, there is no commonly accepted standard for harvesting, isolating, and storing BMMSCs. Protocol variability alone could explain the heterogeneity in outcomes between studies. There is also no agreement on what constitutes a suitable placebo. The small amount of bone marrow used in the placebo in REGENERATE-AMI could have affected myocardial healing, thereby diluting the treatment effect. In addition, post-conditioning due to the BMMSCs administration technique itself (occlusion–reperfusion) needs to be considered.

Finally, we must consider that one dose of BMMSCs might not be enough. While there may be a positive effect of BMMSCs on infarct size and LV remodelling, it appears either modest or possibly transient, as suggested by the REGENERATE-AMI. If so, multiple stem cell injections may be needed to ensure a long-lasting benefit of BMMSCs therapy. The ongoing phase III REPEAT trial (ClinicalTrials.gov identifier: NCT01693042) is designed to answer this question in chronic HF patients and will require testing in the setting of AMI.

It is also increasingly uncertain what impact BMMSCs will have on mortality and hard cardiovascular clinical endpoints in an era where the case fatality rate of AMI has fallen dramatically in the last decades. Against this background, the results of Afzal et al.\(^16\) may no longer stand, and the vast majority of studies using BMMSCs to

![Figure 1: Factors affecting the bone marrow cells effect on cardiac recovery after acute myocardial infarction. LV, left ventricle; MACE, major adverse cardiac events.](image-url)
date have lacked the statistical power to test hard clinical endpoints. The BAMI trial (ClinicalTrials.gov identifier: NCT01569178) is an ongoing European multinational, multicentre, randomized open-label, controlled, parallel-group phase III study targeting 3000 patients and testing the effect of BMMSCs on total mortality up to 3 years of follow-up.

From REGENERATE-AMI, one can only conclude that early BMMSCs administration is safe and feasible. Ongoing research presently aims to identify other cell sources, paracrine-acting proteins, and techniques designed to improve stem cell homing in the infarcted myocardium. Future research must seek to elucidate the optimal patient population, composition of stem cell isolates, bench techniques, timing, and dosage specific to the setting of AMI.

Conflict of interest: none declared.

References