Current clinical trials of cell-based therapies in cardiac repair: too many variables spoil the stem cell broth

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This editorial refers to 'Impact of intracoronary bone marrow cell therapy on left ventricular function in the setting of ST-segment elevation myocardial infarction: a collaborative meta-analysis', by R. Delewi et al., on page 989

Even the staunchest advocate of the use of cell-based therapies in cardiac repair would be forced to admit that progress has thus far been slow. Both use of therapeutic stem cells and gene-based approaches have met with significant hurdles in their clinical development. However, significant progress does continue to be made towards the ultimate goal of a safe and efficacious cell-based therapy for routine clinical use in cardiac repair.

In the area of stem cells, a number of approaches have been proposed, tested pre-clinically, and then clinically evaluated, albeit in relatively small studies thus far. These include use of skeletal muscle myoblasts (SKMs), bone marrow-derived mononuclear cells (BMCs), mesenchymal stem cells (MSCs, both bone marrow and adipose tissue derived), and cardiac stem cells. Amongst these, the most rigorously evaluated thus far have undoubtedly been the BMCs. Bone marrow-derived mononuclear cells used therapeutically may be unselected or selected according to characteristic cell surface markers, e.g. CD34, CD133, and/or CXCR4, amongst many other identifiers. Putative mechanisms of benefit of BMCs in the post-myocardial infarction (MI) cardiac repair setting have been variously ascribed to both direct transdifferentiation into cardiomyocytes (likely to play only a minimal, if any, role), indirect actions such as vasculogenesis and angiogenesis, antiapoptotic and antinecrotic effects, and favourable paracrine effects on the extracellular matrix.

Intravascular delivery methods invariably result in only minimal local accumulation and retention of cells within the heart in general and the peri-infarct region specifically post-MI. In addition, the cardiac microenvironment in the early post-infarct setting is relatively hostile to stem cell engraftment and differentiation, with local proinflammatory cytokine activation further diminishing therapeutic activity of delivered cells. Further, the presence of cardiac disease itself, not to mention the co-morbidities commonly associated with it, including advanced age, appear to impair the ability of stem cells to release critical homing and engraftment factors, e.g. stromal cell-derived factor-1, that may be contributory to their success in cardiac repair.

Nevertheless, despite the above seemingly major limitations to the potential benefit of these cells post-MI, advances have been made with BMCs in this setting. Delewi and colleagues have now undertaken a collaborative meta-analysis whereby original data were sent to the researchers from the individual contributing BMC study groups. This approach, although time consuming, is vastly superior to conventional meta-analysis where group data from individual studies are pooled, with inferences often having to be made regarding data not readily extractable from the relevant publication. This collaborative approach therefore permits a more robust and probably more accurate analysis of the true impact of BMCs in the post-MI setting as well as the ability to cut the data into relevant subgroups to generate hypotheses of clinical and mechanistic interest.

The key findings of the meta-analysis were modest beneficial effects on the post-MI left ventricular (LV) remodelling process, specifically increased LV ejection fraction (LVEF) and reductions in LV end-systolic and end-diastolic volume index (LVESVI and LVEDVI). Furthermore, subgroup analysis supported younger patients (perhaps because of better preservation of stem cell functional capacity) and those with lower baseline LVEF as having the greatest antiremodelling benefit. Interestingly, timing of administration in relation to the occurrence of the acute coronary syndrome (ACS) event as well as the subsequent percutaneous coronary intervention did not appear to be particularly critical regarding subsequent remodelling endpoints, suggesting that any putative benefits of early administration of stem cells may be offset by loss of quality of therapeutic cells in the immediate post-MI proinflammatory environment. For this reason, temporal remoteness from MI such as in the chronic

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LV systolic dysfunction or ischaemic cardiomyopathy setting may be preferred for stem cell cardiac repair, although this hypothesis needs more rigorous testing.

Not highlighted in this analysis but clear from the individual trial data is the large degree of heterogeneity in the study results observed. This is supported by earlier conventional meta-analyses reporting on similar LV remodelling-type endpoints. The large variation in remodelling responses probably reflects the huge variability in study characteristics of the individual trials, including patient population, trial design and mode of administration of the mononuclear cells (MNCs). Specifically, MNC trials have included patients of varying age following an ACS event, receiving a variety of BMC subtypes over a large range of cell numbers, and given any time from 1 to 28 days post-ACS event with follow-up as short as 3 months post-administration. Although this analysis included only BMC trials where the cells were administered via the intracoronary route, other studies have included alternative delivery modes including systemic intravenous as well as direct intramyocardial injection. Various forms of cell processing have been utilized in some studies, with BMCs co-cultured with growth factors such as granulocyte colony-stimulating factor.

It is thus almost inevitable that such a heterogeneous series of relatively small studies would result in widely variable individual trial findings. This is compounded by entry criteria permitting patients with relatively preserved LV systolic function and chamber size to be included then analysed for improvements in remodelling parameters using a variety of imaging modalities. Indeed, in many studies meta-analysed, only a minority of patients had an LVEF <45%. Clearly it is difficult to improve an ejection fraction or LV volume that is almost normal to begin with. Choice of patients deemed most likely to benefit from a specific therapy matched to clinically appropriate and meaningful trial endpoints accurately measured is a cornerstone of study design for any intervention. With regard to endpoint accuracy, it is noteworthy that not all trials utilized an imaging core laboratory in endpoint evaluation. Furthermore, in improving precision of remodelling evaluation, choice of imaging modality may also be critical. Cardiac magnetic resonance imaging (cMRI) provides more accurate information regarding LV volumes and function than echocardiography or single-photon emission computed tomography (SPECT). Furthermore gadolinium-based cMRI protocols that provide quantitative information regarding fibrosis status post-MI may be useful in prediction of longer term prognostic benefit of BMCs (and perhaps other therapeutic stem cell types). Notwithstanding the above and given the uncertain status of systolic LV function in the immediate post-MI period (stunning, hibernation), more clinically relevant surrogate endpoints such as exercise capacity and quality of life should be considered in early phase trials of stem cells going forward.

As mentioned, additional to BMCs, other stem cell types are being actively explored in cardiac repair (Figure 1). SKMs have been associated with serious ventricular arrhythmias in early studies, requiring an implantable cardiac defibrillator for later trials. MSCs are...
immune-privileged (hypoimmunogenic) cells allowing for potential allogeneic delivery which would theoretically permit ‘off the shelf’ use. Data support improvements in remodelling parameters similar to that of BMCs, with head to head allogeneic vs. autologous studies also yielding not dissimilar results (for both efficacy and safety, notably low rates of donor-specificalloimmune reactions). Finally, c-kit$^+$ and cardiosphere-derived autologous cardiac stem cells have also been the subject of (small) remodelling studies, with encouraging results.

In all of these assessments, it has to be remembered that the above parameters are surrogate endpoints that are not invariably predictors of ultimate major clinical outcome success of a therapy. Furthermore, short-term remodelling effects do not necessarily persist, even within the same BMC trial. For all of the above reasons, what is ultimately required are rigorously designed, adequately powered studies of clinically meaningful endpoints such as re-infarction, cardiovascular hospitalization, and mortality. Side by side with efficacy assessments is the need for establishment of long-term safety, especially given theoretical concerns about administration of cells triggering cancerous change via stimulation of proangiogenic factors.

Fortunately, such large-scale outcome studies are in the works. The Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells (BM-MNC) on All-Cause Mortality in Acute Myocardial Infarction (BAMI)$^{16}$ is a definitive phase III outcome study of BMCs in post-MI patients with an LVEF of $<45\%$ being conducted in European countries. A large-scale major clinical outcome trial of allogeneic MSCs in patients with established chronic heart failure has been announced but not yet commenced. These and future large-scale studies will cut through the current morass of small trials involving multiple variables that at present constrain our ability to determine readily the optimal stem cell approach to cardiac repair.

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**References**