EDITORIAL

Stem cells to repair the broken heart: much ado about nothing?

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The long promised benefits of using stem cells for myocardial repair are still awaited

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Over the past few years, there has been an almost zealous interest in repairing infarcted myocardium using cell-based therapy. The first step in this journey was challenging the long-held dogma that cardiac myocytes are terminally differentiated and irreplaceable. This challenge occurred through observations in the human heart of myocytes undergoing mitotic division in the peri-infarct zone,¹ and possessing Y-chromosomes in female hearts donated to male recipients.² These coincided with landmark experiments in animals that appeared to demonstrate regenerated myocardium and vasculature following the injection of transgenic bone marrow cells,³ and the genesis of mature endothelial cells from circulating components of peripheral blood.⁴ In combination these observations signified the profound effects multipotent haemopoietic stem cells might have upon the ischaemic or infarcted heart. Could this presage a revolution in the treatment of ischaemic heart disease?

So far, the quest to demonstrate significant improvement in outcomes in patients receiving cell therapy for ischaemic heart disease has been typified by different routes of delivery with varied progenitor cell types and numbers. Nonetheless, the impetus to discover the most effective, unifying, treatment combination remains strong, driven in part by the limitations of the current treatments for patients with substantial myocardial damage.

Given this degree of attention, it is all the more surprising that several key issues remain unclear. In particular, it is not yet established which cell subtypes are most effective as donors, if and how engraftment occurs, what is the optimum timing and method of delivery, and which individuals could benefit most. Broadly, experiments to date may be divided into two categories: non-haemopoietic and haemopoietic stem cell-based therapies. Interestingly, despite these uncertainties, only haematopoietic stem cells have been used so far in acute myocardial infarction (AMI) trials, despite the fact that initial success was achieved using skeletal myoblasts.⁵

SKELETAL MYOBLAST THERAPY FOR CHRONIC ISCHAEMIC HEART DISEASE

Experiments using fetal, neonatal and adult myoblasts from both animals and humans

suggested that transplantation of these cells was technically feasible with many millions of cells being expanded from a small muscle sample. More importantly, such cells improved cardiac function.⁶ However, the mechanisms were unclear and could potentially arise from indirect effects such as donor cell-induced angiogenesis, as opposed to myocardial regeneration per se. This latter hypothesis was supported by evidence of cardiac functional improvement after transplantation of fibroblasts.⁷ The phase I human trials for chronic ischaemia with skeletal myoblasts that followed were promising, with improved symptoms and ejection fraction.⁸ However, some patients developed ventricular tachycardia, possibly as a result of the documented failure of the myoblasts and derived skeletal muscle fibres to integrate.⁹ Now a double-blind randomised phase II trial using skeletal myoblasts is nearing completion (MAGIC II) and may answer some of these questions, but to allay safety concerns all patients are fitted with an internal cardiac defibrillator (ICD).

STEM CELL THERAPY FOR ACUTE MYOCARDIAL INFARCTION

The translation of findings with haemopoietic progenitors from animal models to clinical trials was faster and more prolific than with skeletal myoblasts. Generally, clinical studies are characterised by relatively small numbers, and less than robust controls. An early report from Strauer *et al*¹⁰ seemed to demonstrate a beneficial effect of injecting autologous bone marrow cells into the infarct related artery of 10 patients who had undergone percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) between 5–9 days previously. Improvements were observed in myocardial perfusion in the infarcted territories, as well as enhanced left ventricular wall motion. However, the control group did not undergo a sham bone marrow harvest or vehicle infusion, let alone perfusion scanning, and their ejection fraction was unchanged. By way of contrast, the TOPCARE-AMI study is unique in comparing 20 AMI patients reperfused by PCI who received haemopoietic stem cells prepared from the bone marrow or peripheral blood and then injected down the infarct artery at approximately four days post-AMI.¹¹ The source of progenitor cells

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Abbreviations: AMI, acute myocardial infarction; G-CSF, granulocyte-colony stimulating factor; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; SPECT, single photon emission computed tomography

appeared to make little difference, with both groups having an 8% increase in ejection fraction as measured by ventriculography, as well as increased viability and contractile function, compared to historical controls.

In a slightly larger study, the BOOST investigators examined 60 AMI patients who received either optimum medical therapy or bone marrow cells 4.8 days after primary angioplasty, with an improvement in magnetic resonance imaging (MRI) derived ejection fraction of 6% in the bone marrow group, but again without a sham harvest or infusion.¹² Kang and colleagues pursued a slightly different design in their trial, also named MAGIC, investigating granulocyte-colony stimulating factor (G-CSF) and progenitor cell infusion after PCI for AMI.¹³ The number of patients at six months follow up were relatively small, with seven and three in the cell infusion and G-CSF groups, respectively, and only one in the control group. Interestingly, although myocardial perfusion and ejection fraction improved in the cell infusion group, there was a worryingly high rate of restenosis of the culprit lesion in patients who had received G-CSF. This finding supports the cautionary approach advocated with G-CSF in patients with coronary disease reported by Hill *et al* in 16 patients with stable ischaemic heart disease who received G-CSF. Subsequently, two patients sustained myocardial infarction, one within eight hours, and the other 17 days, after G-CSF exposure, the latter being fatal.¹⁴

In randomised trials that do use controls subjects who receive sham harvest and saline infusion, results appear to differ. Chen *et al* describe an improvement in ejection fraction as well as wall motion and contractility in patients given mesenchymal stem cells approximately 18 days after PCI.¹⁵ By contrast, Janssens' group obtained bone marrow cells just 24 hours after PCI, and despite showing a greater reduction in infarct size and improved regional systolic function, there was no overall improvement in global left ventricular function compared to controls.¹⁶ This disparity may be accounted for by the different times at which bone marrow was harvested, and/or by the huge difference in numbers of cells injected. The study by Chen *et al* delivered two orders of magnitude more cells than the latter equivocal Janssens study, namely 10^{10} versus 10^8 cells, respectively.

So how does the cell therapy study (TCT-STAMI) by Junbo *et al*¹⁷ in this issue of *Heart* fit into this increasingly elaborate landscape? Uniquely, bone marrow aspiration was performed within three hours of PCI in 20 patients, who were then

randomised to receive either the cells or supernatant. Clearly, complications with bleeding from the biopsy site in the context of antiplatelet therapy are an issue, although none was reported. Another original feature is the use of supernatant, thereby controlling for the non-cellular effects of the bone marrow aspirate. Yet at six months after therapy, bone marrow treated patients had an improved ejection fraction (approximately 5%) and perfusion score compared to the supernatant group. Does this provide a new insight into the optimum timing of therapy? Since the high baseline ejection fraction was greater in the supernatant group, the degree of improvement may have been limited and thus statistically insignificant. Similarly, the 5% improvement in ejection fraction was seen in patients whose baseline was greater than 50% to begin with, and perhaps the incremental benefit derived would have been even greater if patients with more extensive myocardial infarction had been included.

A recent study seems to highlight the modest benefits observed in cell therapy trials. Within six hours of AMI, Baks *et al* performed PCI, but without infusion of stem cells.¹⁸ Using contrast enhanced MRI (ce-MRI), ejection fraction at five months was found to have increased by 7%, with a 31% reduction in infarct size, suggesting that intrinsic factors, perhaps including circulating progenitor cell levels, are important determinants of myocardial repair. These findings are consistent with a previously reported observational study of post-AMI patients.¹⁹ Results from the late breaking randomised ASTAMI study have added a further note of caution.²⁰ Patients were randomised to receive either bone marrow cells 4–8 days after anterior AMI, although the control group did not receive a sham procedure or placebo injection. However, at six months there was no difference in ejection fraction or clinical outcomes. Indeed, the MRI derived ejection fraction in the controls showed a trend towards improvement compared to bone marrow cells, although the echo and single photon emission computed tomography (SPECT) derived values did not. An analysis of ejections fraction at baseline and follow-up (table 1) from these studies suggests that the impact of cell therapy so far has been somewhat unremarkable, particularly when randomised trials are considered.

As present, therefore, it would seem imprudent to push forward with yet more small, underpowered, inadequately controlled and improperly blinded progenitor cell trials. Historically, far greater numbers of patients ($n = 188$) have been required to demonstrate significant improvements in

Table 1 Stem cell trials

Trial	Randomised	Method of LVEF assessment	Length of follow up (months)	Group	Mean basal EF (%)	Mean final EF (%)	Change in EF	p Value
BOOST ¹²	Yes	MRI	6	Control, n = 30	51.3	52.0	0.7	
				Active, n = 30	50.0	56.7	6.7	0.026
MAGIC ¹³	Yes	SPECT and echo	6	Control, n = 1	33.0	39.0	6	
				Cells+ G-CSF, n = 7	48.7	55.1	7	0.005
				G-CSF only, n = 3	45.4	44.0	-1.5	0.007
TOPCARE-AMI ¹¹	No	LV angiography	4	Control, n = 11	51.0	53.5	2.5	
				Active, n = 19	51.6	60.1	8.5	0.003
Janssens <i>et al</i> ¹⁶	Yes	MRI and echo	4	Control, n = 34	46.9	49.1	2.2	
				Active, n = 32	48.5	51.8	3.4	0.36
ASTAMI ²⁰	Yes	MRI	6	Control, n = 50	53.6	58.1	4.5	
				Active, n = 50	54.8	56.2	1.4	0.51
TCT STAMI	Yes	Echo	6	Control, n = 10	58.2	56.3	-1.9	
				Active, n = 10	53.8	58.6	4.8	<0.05
Observational studies								
Baks <i>et al</i> ¹⁸	NA	MRI	5	n = 22	48	55	7	<0.05
Ingkanisorn <i>et al</i> ¹⁹	NA	MRI	2	n = 33	52	57	5	<0.002

EF, ejection fraction; G-CSF, granulocyte-colony stimulating factor; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NA, not applicable; SPECT, single photon emission computed tomography.

left ventricular ejection fraction following the administration of intracoronary streptokinase.²¹ In this context, the numbers of patients recruited to demonstrate a benefit in some of the cell therapy studies is surprising. Perhaps what is needed is the seemingly tautologous combination of a large multinational trial and detailed mechanistic benchwork. The large multinational trial will determine whether simply delivering some bone marrow down a coronary artery is of any benefit, while the mechanistic benchwork will enable a scientific basis for the inevitable iterative improvements that will be necessary once the trial results are revealed.

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STAMPS IN CARDIOLOGY

Japanese metal engraving

An unusual philatelic item from Japan is illustrated. The booklet contains the 1972 Japanese stamp for the World Health Organization (WHO) heart campaign of that year with a fine cancellation incorporating the heart (as a similar design to that seen in the stamp) and the WHO logo alongside. The stamp was designed by Masatoshi Hioki. The booklet also contains a metal engraving of the stamp drawings by Hosei Hotta. The text reads "As foundation work, metal engraving of the drawings is done by Hosei Hotta. Then, thick-plating, colouring with various kinds of precious metals, and finishing hand-work are performed".

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