Stem cell therapy in cardiology

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Cell therapy provides one of the most important solutions to the unmet need for new treatments in cardiovascular disease. This area of research has undergone a rapid translation into humans, with the bone marrow mononuclear cell predominating as the cell type with most clinical data. Confidence in the use of this cell type has grown over the last year with the publication of the results of Phase II/III trials in the setting of acute and chronic ischemia confirming safety and biological activity. A large pan-European outcome study is now being planned, which will definitely address the therapeutic potential of this cell type with respect to mortality. Data for the use of selected populations of cells, bioengineered cells/scaffolds and the resident stem cell population continue to grow, with some of these approaches reported in Phase I clinical trials with promising results. There is still some way to go and these more complicated cell therapy products will need to undergo the same scrutiny that has been applied to the results of the bone marrow mononuclear cell trials to date. Ultimately, these engineered biologics will have to justify the costs involved in producing them by significantly improving on results obtained by using bone marrow mononuclear cells for cardiovascular repair. The continued success of this area of translational medicine relies on the ongoing partnership between clinicians and scientists, who have thus far demonstrated a determined and pragmatic approach to solving some of the complexities of moving from bench to bedside. The next 5 years will see this partnership reach fruition as the long-awaited results of outcome studies of cell therapy in the treatment of cardiovascular disease are published.

The goal of regenerative medicine for the heart is the creation of new myocytes to replace the billions of cells that can be lost during myocardial ischemia. The embryonic stem cell (ESC) is still the obvious choice to regenerate damaged myocardium. Basic research continues to establish a better understanding of how to harness the potential of the cell type and turn it into a therapeutic. There is still some way to go before the cells can be safely delivered into humans in a controlled fashion. Likewise, research using induced pluripotent (iPS) cell, which were thought to have all the benefits of the ESC but none of the ethical constraints, has shown that there are new obstacles such as immunogenicity and problems with cell expansion that need to be overcome. Trials involving bone marrow mononuclear cells (BMMNCs) still predominate in the

clinical setting. This is partly due to the natural evolution from the first results reported in the basic scientific literature more than 10 years ago [1] and also a pragmatic approach in which this cell type is currently the easiest to test in humans. As a consequence, the BMMNC has the most safety and efficacy data associated with its use in ischemic heart disease [2,3].

Recent developments

In acute myocardial infarction (AMI) the results of another large clinical trial (HEBE) has reported no significant benefit of cell therapy on the primary end point of cardiac function [4]. The results of this clinical trial are at variance to the original animal experiments that catalyzed the translation into humans and also the results of some of the landmark first clinical trials

performed in this area. Of these original positive studies 'Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration' (BOOST) and 'REPAIR-AMI' stand out since they were the first large-scale trials to show an improvement in cardiac function in patients receiving cell therapy. Both of these trials have recently reported the results of 5-year follow-up.

The BOOST trial originally reported a 6.7% increase in global left ventricular ejection fraction (LVEF) assessed by MRI at 6 months in the treatment group compared with a 0.7% increase in the control group [5]. The 5-year follow-up data assessed whether the infused BMMNCs could have a sustained effect up to approximately 61 months compared with controls [6]. The results demonstrated a decline in LVEF and increase in left ventricular (LV) volumes in both groups over the 5-year period, with no significant difference between treatment and control groups, despite the early promise at 6 months. Furthermore, no

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difference was shown in mortality or other clinical end points between cell therapy and control groups. This study did, however, confirm the safety of the technology used. Interestingly, in line with other trials, subgroup analyses did suggest that cell therapy in more severe infarction (described as greater transmural) conferred a significant benefit in LVEF and LV dimension compared with control. This benefit was not seen in those with an infarct transmural of less than the median.

By contrast, the REPAIR-AMI trial enrolled 204 patients, representing the largest experience in stem cell therapy for cardiac repair to date, and demonstrated a significantly greater improvement in LVEF in those patients treated with BMMNCs compared with placebo at 4 months. Patients with depressed LV functions showed most benefit [7]. This was the first large-scale clinical end point data showing mortality and morbidity benefit conferred by intracoronary administration of progenitor cells, although the study was not sufficiently powered for this purpose. The REPAIR-AMI 5-year follow-up data was presented at the Transcatheter Cardiovascular Therapeutics Conference 2010. A total of 100 patients in each treatment arm were followed at 5 years. In absolute numbers, there were 15 deaths in the placebo group, compared with seven in the cell therapy group, although this does not quite reach significance ($p = 0.07$); however, again there was a sustained significant reduction of the combined end point of death, recurrence of myocardial infarction and revascularization up to 5 years after a single intracoronary infusion of cells.

The results of these two trials indicate that if ejection fraction is used as a surrogate end point, those patients with lower ejection fractions (and hence bigger infarcts) seem to benefit the most. This is in the context of cell administration 5–8 days following AMI. There is still a need to ascertain

whether the earlier or indeed later time points (relative to ischemic insult) may well benefit patients. The earlier time point is currently being addressed by the REGENERATE-AMI clinical trial (EUDRACT 2007–002144–16) that is over halfway through recruitment and will report in 2013. In this trial, patients with AMI are receiving cell therapy (BMMNC) approximately 6 h after their angioplasty. The TIME, Late-TIME and SWISS-AMI trials aim to evaluate the further time points of intracoronary BMMNC administration post-AMI (TABLE 1).

One of the most important developments over the last year is the move from Phase II clinical trials into Phase III. To date, the majority of clinical trials have been designed to assess safety and feasibility, with efficacy measured using a surrogate end point such as ejection fraction looking for ‘activity’. The modest positive effects of cell therapy on ejection fraction have led to considerable debate as to whether this is a meaningful result for patients. Indeed the magnitude of effect is similar to that seen when the landmark studies of current therapeutic agents (e.g., primary angioplasty, angiotensin-converting enzyme inhibitors, and β -blockers) are retrospectively analyzed using ejection fraction as the end point. These trials all demonstrated significant benefits in mortality and morbidity associated with similar small improvements (if any) in cardiac function, as seen in the cell therapy trials published to date [8]. In order to address this issue the EU funding program (FP7) recently awarded a consortium composed of 17 clinical centers across Europe (the BAMI consortium) funds of €6 million to design and conduct the definitive outcome (mortality) study of BMMNC in AMI. The trial will enroll approximately 3000 patients and is one of the most exciting developments in the field for several years. The results of this study will be reported in 5 years.

Moving from acute to chronic ischemia, the results of the largest (nonrandomized) study assessing the effect of BMMNCs in chronic heart failure – the European STAR-heart study – were reported in 2010 [9]. Here 391 patients with ejection fractions of 35% or less were offered intracoronary administration of autologous BMMNCs. A total of 191 patients participated and 200 (who refused cell therapy) were followed-up with best medical treatment alone. There was a significant improvement in LVEF, contractility, oxygen uptake and exercise tolerance from 3 months through to 5 years in the treated group. Most interesting was the mortality data, which showed that over the follow-up period of 5 years, seven patients died in the treated group, whereas 32 patients died in the control group. This suggests a considerable mortality benefit, indicating again the need to conduct double-blind randomized clinical trials to confirm this possibility.

The FOCUS-HF trial [10] evaluated the effects of transendocardial BMMNC delivery in patients with chronic ischemic heart failure with no further revascularization option. The study consisted of 30 patients randomized to either cell-treated or control groups and follow-up was 6 months. Cell therapy was found to significantly improve symptoms and quality of life scores and in subgroup analysis oxygen uptake in patients who were 60 years and younger.

The majority of trials outlined above have focused on the use of cell therapy to restore or repair myocardial infarction following either acute or chronic ischemic insult. Another area of unmet need is for the patient with refractory angina despite best medical therapy and full revascularization. The last year has seen some of the small studies (Phase I) start to report with promising results. Several trials showed beneficial effects of autologous cell therapy on a variety of parameters, including myocardial perfusion, angina

symptoms and quality of life measures up to 1 year [11–13]. A US trial, FOCUS, is of similar design to FOCUS-HF and looks at the safety and efficacy of transendocardial BMMNCs in chronic ischemia patients with depressed ejection fractions and refractory angina with no revascularization option. The outcome measures include myocardial perfusion, LV contractility and oxygen consumption and follow-up is to 5 years.

Although unfractionated bone marrow-derived cells constitute the majority of clinical data reported to date, fractionation/cell-selection has also been used to identify a specific phenotype that can be used for myocardial repair. More lineage-determined stem/progenitor cells such as CD34⁺ cells (either bone marrow-derived or circulating) have been assessed in clinical trials for their ‘regenerative’ capability. The randomized controlled REGENT trial showed no difference in LVEF between the bone marrow-derived CD34⁺ cell-treated group, the unfractionated BMMNC-treated group or the placebo group after intracoronary injection postmyocardial infarction at 6 months, suggesting that careful consideration must be given to the choice of cell type if antigenic selection is used [14]. The results of studies using CD133⁺ cells (putative marker of endothelial progenitor cells) are awaited.

Owing to the ability of the mesenchymal stem cell (MSC) to differentiate into various cell types that may contribute to restoring myocardial function and the relative ease of access to this cell (bone marrow and adipose tissue) the results of clinical trials using MSCs are starting to emerge again with promising preliminary findings (TABLE 1). The 18-month results of the first-in-human 14-patient trial of autologous adipose tissue-derived stem and regenerative cells for AMI, APOLLO, were reported at the recent 2011 International Symposium on Stem Cell Therapy & Cardiovascular Innovation [15]. All patients in the treatment arm received cell therapy

within 24 h of primary percutaneous coronary intervention. They were first-MI patients with an estimated ejection fraction between 35 and 50%. At both 6 and 18 months there was a significant reduction in infarct size and improvement in estimated ejection fraction with cell therapy compared with control, and the treatment proved safe. A trial using adipose tissue-derived stem and regenerative cells for patients with heart failure has also reported positive improvements in symptoms (PRECISE, presented at the International Symposium on Stem Cell Therapy and Cardiovascular Innovation 2010). Interestingly, at 6 months there was no difference in LV function but infarct size in the treated group was found to be reduced compared with a relative significant increase in that of the control group. Furthermore, there was a significant improvement in metabolic equivalents and peak oxygen consumption in the treated group up to 18 months.

Allogeneic as opposed to autologous MSCs have also recently been evaluated as a potential novel therapeutic strategy allowing an ‘off-the-shelf’ cell-based therapy to circumvent the practical limitations of cell harvesting and *ex vivo* culture present in the autologous setting. MSCs exert anti-inflammatory and anti-apoptotic effects, and lack MHC class 2 molecules, meaning they are unlikely to create an immune response and so immunosuppression is not required for these patients. The first-in-human Phase I study by Hare *et al.* enrolled 53 patients after first AMI with estimated ejection fractions between 30 and 60%, randomized into either treatment or control groups [16]. Importantly, the study demonstrated no difference in adverse events, rehospitalization or arrhythmia. In terms of efficacy data there was a significant difference in LV function in the treated group compared with the control group up to 18 months follow-up. Dib *et al.* reported on the 3-month results of a similar trial assessing transendocardial allogeneic MSC

administration in chronic heart failure at the 2010 International Symposium on Stem Cell Therapy & Cardiovascular Innovation. Their findings again confirmed safety of the technology and significant improvements in LV function in the treated group compared with decline of LV function in the control group. The MSC has also recently demonstrated important functional benefits in patients with heart failure, suggesting that this cell type provides an important therapeutic potential that needs evaluation in larger-scale clinical trials [17].

Perhaps the most novel technology to be utilized and evaluated in cardiovascular clinical trials to date is that of the C-Cure trial reported at the American College of Cardiology i2 conference 2011. Here the investigators have driven the differentiation of BMMNCs into lineage-specific cardiac progenitor cells using cardiogenesis proteins before cell transfer via the transendocardial route. In total, 45 patients with chronic heart failure were enrolled and randomized to treatment or control arms of the study. Importantly, there were no observed significant differences in adverse outcome. In the treatment group there was a significant improvement in LVEF and reduction of LV volumes up to 6 months. Furthermore, there was a sustained improvement in symptoms exemplified by the significant improvement in the 6-min walk test compared with the decline over the same time period in the control group.

While cell therapy offers the most direct and often simplest method of developing a new therapeutic approach to restore myocardial function, other derivatives and byproducts of this approach are also under evaluation. Initial observations suggesting that only a small number of cells are retained has led to the development of various gels and matrix-like compounds that have the potential to improve engraftment as well as having some direct benefits

Table 1. Ongoing and recently reported clinical trials assessing cell-based therapy in ischemic heart disease.

Trial	Year reported	Type of trial	Patients (n)	Cell type
BOOST. 5-year follow-up Intracoronary bone marrow cell transfer after myocardial infarction: 5-year follow-up from the randomized controlled BOOST trial	2009	Phase I RCT	60	Autologous BMMNCs
REPAIR-AMI. 5 years and counting	2010	Phase III RCT	200	Autologous BMMNCs
SWISS-AMI Cell-based therapy for myocardial repair in patients with acute myocardial infarction: rationale and study design of the Swiss multicenter intracoronary stem cells study in acute myocardial infarction	In progress	Phase II RCT	194	Autologous BMMNCs
TIME A Phase II, randomized, double-blind, placebo-controlled pilot trial evaluating the safety and effect of timing of administration of bone marrow mononuclear cells following acute myocardial infarction	In progress	Phase II RCT	120	Autologous BMMNCs
LateTIME A Phase II, randomized, double-blinded, placebo-controlled, pilot trial evaluating the safety and effect of administration of bone marrow mononuclear cells 2–3 weeks after acute myocardial infarction	In progress	Phase II RCT	87	Autologous BMMNCs
The STAR Heart study The acute and long-term effects of intracoronary stem cell transplantation in 191 patients with chronic heart failure	2010	Non-randomized	391	Autologous BMMNCs
FOCUS-HF A randomized study of transendocardial injection of autologous bone marrow mononuclear cells and cell function analysis in ischemic heart failure	2011	Phase II RCT	30	Autologous BMMNCs
FOCUS Intramyocardial injection of autologous bone marrow mononuclear cells for patients with chronic ischemic heart disease and left ventricular dysfunction	In progress	Phase II RCT	87	Autologous BMMNCs
APOLLO A randomized clinical trial of adipose-derived stem cells in the treatment of patients with ST-elevation myocardial infarction	2011	Phase I RCT	14	Autologous MSCs
PRECISE A randomized clinical trial of adipose-derived stem cells in treatment of nonrevascularizable ischemic myocardium	2010	Phase I RCT	36	Autologous MSCs
Hare et al. A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (Prochymal®) after acute myocardial infarction	2009	Phase I RCT	53	Allogeneic MSCs
Dib et al. The first US study to assess the feasibility and safety of endocardial delivery of allogeneic mesenchymal precursor cells in patient with heart failure: 3-month interim analysis	2010	Phase II RCT	60	Allogeneic MSCs
C-CURE Lineage-specific bone marrow derived cardiopoietic mesenchymal stem cells for treatment of ischemic cardiomyopathy	2011	Phase I RCT	45	Cardiopoietic MSCs

AMI: Acute myocardial infarction; BMMNC: Bone marrow mononuclear cell; CCS: Canadian Cardiovascular Society; ICD: Implantable cardioverter defibrillator; LV: Left ventricular; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end systolic volume; MACE: Major adverse cardiac events; MSC: Mesenchymal stem cell; NYHA: New York Heart Association; RCT: Randomized controlled trial.

Acute vs chronic ischemia	Primary end point	Secondary end point	Clinical trial identifier
Acute ischemia	LVEF at 5 years	Mortality at 5 years	NCT00224536
Acute ischemia	Mortality, AMI, revascularization, rehospitalization for heart failure at 5 years	Combined clinical end points 5 years	NCT00279175
Acute ischemia	LVEF at 4 months	LVEF, infarct size, perfusion defect, MACE at 12 months	NCT00355186
Acute ischemia	LVEF at 6 months	Death, repeat revascularization at 2 years	NCT00684021
Acute ischemia	LVEF at 6 months	Combined end point (death, reinfarction, repeat revascularization, hospitalization for heart failure, ICD placement), LV mass, LVEDV, LVESV, Infarct size at 6 months	NCT00684060
Ischemic heart failure	LVEF, exercise capacity, oxygen uptake, LV contractility at 3 months	Mortality at 5 years	
Ischemic heart failure	CCS/NYHA functional assessment, oxygen uptake, LVEF, degree of ischemia at 6 months		NCT00203203
Chronic ischemia	Oxygen uptake, LVESV, perfusion defect at 5 years	MACE, CCS, LV wall motion at 5 years	NCT00824005
Acute ischemia	Major adverse cardiac and cerebral events at 18 months	LVEF, perfusion defect, infarct size at 18 months	NCT00442806
Ischemic heart failure	Major adverse cardiac and cerebral events at 18 months	CCS/NYHA functional assessment, oxygen uptake, LVEF, infarct size at 18 months	NCT00426868
Acute ischemia	Adverse event rate at 18 months	LVEF, LVESV, LVEDV at 18 months	NCT00114452
Ischemic heart failure	Adverse event rate at 3 months	NYHA functional assessment, LVEF, LVESV, MACE at 3 months	NCT00721045
Ischemic heart failure	Adverse event rate at 6 months	6-min walk test, LVEF, LVESV, LVEDV at 6 months	NCT00810238

on myocardial function themselves. Similarly, the concept that by providing a platform for cells to exert direct or indirect effects on improving cardiac function has led to the development of bioscaffolds and cell sheet technology. Again, these techniques are undergoing evaluation in preclinical trials and some promising preliminary data in humans are becoming available. Given the complexities in delivering some of these products the beneficial effects on cardiac function will need to be significantly superior to that seen using cell therapy alone. The ultimate incarnation of these concepts is the construction of decellularized donor hearts repopulated with cells from the recipient [18]. If achievable, this solution will overcome the majority of problems that cell therapy alone or its derivatives have encountered. This solution would directly replace the current transplant program, although the availability of donor hearts remains an issue for both. This problem may be overcome using xenograft material. Translation of this promising solution into humans still lies some way off.

Future perspectives

Currently the bone marrow provides the best source cell types to “mend a broken heart”. This is in spite of the disappointing failure to reproduce the dramatic effects on cardiac function seen in animal models. What may have been lost in translation is not the mechanistic benefit of bone marrow-derived cells but our understanding of surrogate end points such as cardiac function. It may well be that in humans, the subtle improvements in cardiac function as shown in trials of cell therapy to date will translate into significant mortality and morbidity reductions. This can only be addressed by designing trials with ‘meaningful’

clinical end points. The next 5 years will see such trials proliferate. The BAMi trial of bone marrow-derived cells in AMI will be one of the first to use mortality as an end point and has been perceived as one of the most important advances in the field of cell therapy in humans.

The partnership between basic scientists and clinicians will continue to see the development of cell types with enhanced therapeutic potential. The C-Cure trial has put down an important marker for the field of modified cells. However, this approach will still need to follow the path that the trial of bone marrow-derived cells has taken. This will eventually lead to the design of large outcome studies. Given the costs and complexities involved in producing these cells, the results obtained from use of engineered cells will need to be vastly superior to the benefits seen with bone marrow cells.

Another approach that will be developed through a better understanding of the mechanisms involved in cardiac repair will allow targeting of paracrine mechanisms and survival pathways using new techniques such as miRNAs. Mechanistic insights into the control of the resident stem cell population will also

offer potential therapeutic options [19]. No-one underestimates the complexities that are involved in these approaches and it will take time and patience to achieve therapeutic success in humans. Likewise, although our understanding of the ESC is increasing, so too is our knowledge of the technical and ethical issues that need resolving before this, the ultimate cell type for cardiac repair, can be safely used to treat human beings.

What is of utmost importance is that the strong partnerships that have come about between scientists and clinicians are nurtured and encouraged so that cell therapy for cardiovascular disease will continue to set the example of how to deliver true translational science.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key points

- Cardiovascular disease claims more lives than any other illness.
- Cell therapy offers a novel solution for the unmet need to develop new treatments for cardiovascular disease.
- The embryonic stem cell and induced pluripotent stem cell offer the most theoretical benefit for cardiovascular regeneration.
- Bone marrow-derived cells remain the most widely used cell type in cardiovascular clinical trials.
- The results of clinical trials of bone marrow-derived cells continue to demonstrate safety and some biological activity.
- The first Phase III all-cause mortality trial of bone marrow-derived cells in acute myocardial infarction has received funding and will provide a definitive answer to the therapeutic use of this cell type.

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