ALMANAC 2012, THE NATIONAL SOCIETY JOURNALS PRESENT SELECTED RESEARCH THAT HAS DRIVEN RECENT ADVANCES IN CLINICAL CARDIOLOGY

CELL THERAPY IN CARDIOVASCULAR DISEASE

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Abstract

The rapid translation from bench to bedside that has been seen in the application of regenerative medicine to cardiology has led to exciting new advances in our understanding of some of the fundamental mechanisms related to human biology. The first generation of cells used in phase I-II trials (mainly bone marrow mononuclear cells) are now entering phase III clinical trials with the goal of producing a cell based therapeutic that can change the outcome of cardiac disease. First generation cell therapy appears to have addressed safety concerns as well as showing 'activity' in numerous published meta-analyses. With the knowledge gained to date, the field is moving towards the next generation of cells - the 'engineered' cell - that have been developed to display a phenotype that will further enhance the myocardial repair/salvage process. This almanac review covers the latest basic research that may soon have application to humans as well as the results of the latest clinical trials.

Update on cell therapy for the treatment of cardiovascular disease

Cell therapy is one of the most important 'new horizons' in cardiovascular disease. It offers new opportunities to develop therapeutics that could revolutionise the way we treat patients and a field of research that combines an increased understanding of the pathophysiology of the cardiovascular disease with some of the most basic biological concepts involved in embryology. The resultant growth of preclinical research in the cardiovascular system and the rapid translation into humans have led to benefits for human biology as a whole. The field is rapidly advancing; here, we present key developments in the last 2 years. In order to reflect the synergy between basic and translational research, this review is therefore divided into two sections.

Basic science update on cell therapy in cardiovascular disease

New models enhancing our understanding of regeneration Zebrafish

There is a long history of research on amphibian heart regeneration with the most adopted model the zebrafish given its substantial regenerative capacity and amenability to genetic manipulation. The zebrafish heart fully regenerates after the surgical amputation of the cardiac apex: an injury that corresponds to a loss of approximately 20% of the total ventricular mass.[1] Initial experiments suggested that undifferentiated progenitor cells were the principal source of regenerating cardiomyocytes in zebrafish; however, two recent gene mapping studies clearly demonstrate that preexisting committed cardiomyocytes are instead the main source.[2 3] These two groups independently generated transgenic zebrafish in which the cardiomyocyte-specific cmlc2 (also known as myl7) promoter drives the expression of tamoxifen-inducible Cre recombinase. These animals were crossed with a reporter line in which Cre-mediated excision of a loxP-flanked stop sequence induces constitutive expression of green fluorescent protein (GFP). In the offspring of this cross, all pre-existing cardiomyocytes and their progeny were induced to express GFP by tamoxifen treatment. Therefore, if the regenerated myocardium was derived from undifferentiated progenitor cells, the new ventricular apex should be GFP$^-$. Instead, both groups found that the vast majority of the newly regenerated cardiomyocytes were GFP$^+$, suggesting that the heart regeneration in zebrafish is principally mediated by the proliferation of pre-existing cardiomyocytes. This is contrary to the previously held belief that the generation of new cardiomyocytes from stem cells was the underlying aetiology.

Mice versus zebrafish

Although they lack the regenerative capacity of the zebrafish heart, postnatal mammalian hearts also undergo a degree of cardiomyocyte renewal during normal ageing and disease. Recently, a study[4] showed that the differences between mammalian and fish hearts may not necessarily apply early in development. Using approaches from the zebrafish model, the authors resected the left ventricular (LV) apex of 1-day-old neonatal mice and observed a brisk regenerative response similar to that in the adult zebrafish. By 3 weeks after injury, the defect had been replaced by normal myocardial tissue, which showed normal contractile function by 8 weeks. Genetic fate-mapping studies indicated that this regeneration was mediated by the proliferation of pre-existing cardiomyocytes, again as in the zebrafish. Notably, this regenerative capacity was not observed in 7-day-old mice, suggesting that its loss may coincide with cardiomyocyte binu- cleation and reduced cell-cycle activity. Nonetheless, this study indicates that zebrafish-like regenerative mechanisms are latent in mammalian hearts. It also provides a genetically tractable model for dissecting the blocks to these mechanisms in the mammalian adult.

Alternative sources of cardiomyocytes: new concepts and advanced understanding

Fibroblasts as source of cardiomyocytes

It has recently been demonstrated that fibroblasts in infarcts could potentially be reprogrammed directly to cardiomyocytes. Fifteen years ago, researchers showed that fibroblasts could be differentiated into skeletal muscle in vitro or in the injured heart by overexpressing the gene encoding the myogenic transcription factor, MyoD. However, despite extensive work, no comparable master gene for cardiac muscle was found, and interest in reprogramming waned. Spurred by the discovery of induced pluripotent stem cells (iPSCs), scientists have now returned to this field, using combinations of transcription factors to reactivate core transcriptional networks of desired cell types. In the last 2 years, two groups have made progress to this goal. The first group[5] screened a total of 14 cardiac transcription factors finding that a specific combination of three transcription factors, Gata4, Mef2c and Tbx5, was sufficient to generate functional beating cardiomyocytes directly from mouse postnatal cardiac or dermal fibroblasts and that the induced cardiomyocytes were globally reprogrammed to adopt a cardiomyocyte-like gene expression profile. These factors activated the transgene in 20% of fibroblasts of which approximately 4% of the cells expressed endogenous sarcomeric proteins such as cardiac troponin T, with ~ 1% showing functional properties such as spontaneous beating. Thus, most of the cells were only partially reprogrammed, although their global gene expression patterns had shifted markedly from fibroblast to cardiomyocyte.

The second group[6] used a different method of reprogramming mouse embryonic fibroblasts to cardiomyocytes. They used the 'Yamanaka factors'-OCT4 (also known as POU5F1), SOX2, KLF4 and c-MYC-to initiate reprogramming, but then blocked signalling through the JAK-STAT pathway, which is required for pluripotency in the mouse, and added the cardiogenic factor BMP4. These modifications yielded minimal generation of iPSCs, but instead activated the cardiac progenitor programme and, within 2 weeks, generated substantial numbers of beating colonies. By 18 days after induction, approximately 40% of the cells expressed cardiac troponin T. It should be noted that this study used mouse embryonic fibroblasts, whereas Leda et al[5] principally used postnatal mouse cardiac fibroblasts. Reprogramming the scar-forming fibroblast to a cardiomyocyte is appealing, particularly if it can be done directly in the infarct. To succeed clinically, we need to know how normal these reprogrammed cardiomyocytes are, and the process will have to be much more efficient and transgene-free.

Induced pluripotent stem cells

A recent report in Heart drew attention to the great promise of iPSC (reprogrammed somatic cells) as a renewable source of autologous cells.[7] These cells were first discovered only 5 years ago by Takahashi and Yamanaka[8] following the introduction of genes into adult mouse cells reprogramming them to resemble embryonic stem (ES) cells. Given that the DNA of such cells is identical to that of the patient, it has been assumed that they would not be attacked by the immune system although their immunogenicity has not been vigorously examined. However, a study[9] published in Nature in 2011 showed that in a mouse transplantation model, some iPS cells are indeed immunogenic, raising concerns about their therapeutic use. This study examined the immunogenicity of mouse iPS cells, using a teratoma-formation assay. They injected iPS cells into mice that were either immune-compromised or genetically matched with the donor cells. This normally results in the formation of benign tumours called teratomas, which consist of many types of differentiated cells. The approach was validated using a line of genetically matched (autologous) ES cells which gave rise to teratomas, whereas a line of unmatched ES cells was rejected before teratomas were produced. The transplantation of autologous iPS cells derived from fetal fibroblasts into matched mice resulted in the rejection of teratomas, irrespective of the approach used to generate the IPS cells, indicating that, in this assay, matched iPS cells are more immunogenic than matched ES cells.

The study also identified the antigens that may have caused immune rejection of the iPS cells, discovering a group of nine genes that were expressed at abnormally high levels. Inducing the expression of three of these genes (Hormadl, Zgl6 and Cyp3a11) in the non-immunogenic ES cells significantly impaired the cells' ability to form teratomas on transplantation into genetically matched mice. This study provides more questions than answers with many limitations in relation in clinical studies; however, it highlights that a great deal needs to be understood about the mechanisms underlying cellular reprogramming and the inherent similarities and differences between ES cells and iPS cells.

Adjunctive therapies to improve stem cell differentiation

As a related spin-off to cell therapy, two new approaches to cardiac repair have been reported.

Thymosin b4

One of the most exciting developments in regenerative medicine over the past 2 years has been the identification of 'bona fide source of myocardial progenitors' (epicardial derived cells)[10] which can be induced by thymosin b4 to differentiate into cardiomyocytes. This landmark study by Smart et al[11] provides a major step forward in identifying a viable source of stem/ progenitor cells that could contribute to new muscle after ischaemic heart disease and acute myocardial infarction (AMI). They demonstrated that in a mouse model the adult heart contains a resident progenitor cell population, which has the potential to become terminally differentiated cardiomyocytes after MI. Progenitor cells were primed with a peptide called thymosin β4 which induced embryonic reprogramming resulting in the mobilisation of this population and subsequent differentiation to give rise to de novo cardiomyocytes. Following experimentally induced MI, these cells were shown to migrate to the site of injury and then differentiate without any evidence of cellular fusion into structurally and functionally active cardio- myocytes. These cardiomyocytes showed evidence of gap junction formation with adjacent cells, synchronous calcium transients and the formation of operational contractile apparatus. Despite a low overall fraction of these cells being present at the site of injury and a relatively poor overall efficiency of differentiation, serial MRI scans revealed significant improvements in ejection fraction, cardiac volumes and scar size in comparison with sham treated animals. The pretreatment with thymosin β4 was crucial to these effects and may suggest a new strategy for promoting myocardial repair in humans.

MicroRNAs

MicroRNAs (small non-coding RNAs) play a critical role in differentiation and self-renewal of pluripotent stem cells, as well as in the differentiation of cardiovascular lineage cells. As a result, microRNAs have emerged as potential modulators of stem cell differentiation; specifically, miR-1 has been reported to play an integral role in the regulation of cardiac muscle progenitor cell differentiation. A study published in 2011[12] looked to take this one step further and assessed whether the overexpression of miR-1 in ES cells (miR-1-ES cells) enhances cardiac myocyte differentiation following transplantation into the infarcted myocardium. In this study, mice models of MI had miR-1-ES cells, ES cells or culture medium (control) transplanted into the border zone of the infarcted heart. Overexpression of miR-1 in transplanted ES cells protected host myocardium from MI-induced apoptosis through activation of p-AKTand inhibition of caspase-3, phosphatase and tensin homologue, and superoxide production. A significant reduction in interstitial and vascular fibrosis was quantified in miR-1-ES cells compared with control MI. Finally, mice receiving miR-1-ES cells had significantly improved heart function compared with respective controls. This would suggest that miR- 1 drives cardiac myocyte differentiation from transplanted ES cells and inhibits apoptosis post-MI; however, importantly with respect to fibrosis no statistical significance between miR-1-ES cell and ES cell groups was observed suggesting further study in this area is needed. A review[13] of the current evidence for the role of microRNAs in stem/progenitor cells and cardiovascular repair has recently been published.

Clinical update on cell therapy in cardiovascular disease

The translational path from preclinical observation to new treatment development can take many years, even decades. Ten years after the first clinical application of stem cells in cardiac disease,[14] many questions regarding cell types and their administration have been addressed and researchers are better understanding this area of research and the challenges of translational medicine.

Although many candidate cell types for myocardial repair exist, a pragmatic approach has been used in clinical trials which have utilised autologous bone marrow mononuclear cells (BMMNCs) and some of the component cell types found therein (haematopoeitic stem cells, mesenchymal stem cells (MSCs) and endothelial progenitor cells) in the first steps into the clinical setting.[15] Recent years have seen several phase I-II clinical trials of BMMNC transplantation in cardiac disease which have demonstrated safety and feasibility while reports of efficacy, although less consistent, have provided grounds for further investigation.

Recent developments in the use of autologous bmmncs

The last 2 years has seen the some of the larger trials examining BMMNCs in the setting of AMI report long-term results confirming safety to 3-5 years. Reassuringly, recent meta-analyses to look at these studies have again confirmed a small but important 'activity' of cell therapy in improving various surrogate parameters of cardiac function.[16 17]

The first randomised controlled trial of stem cell therapy in AMI was the BOOST trial (BOne marrOw transfer to enhance ST-elevation infarct regeneration) reporting a 6.7% increase in global left ventricular ejection fraction (LVEF) in the treatment group compared with a 0.7% increase in the control group at 6 months; this was attributed to improved regional systolic wall motion in the infarct zone.[18] The 5-year follow-up data[19] showed a decline in LVEF and increase in LV volumes in both groups with no significant difference in mortality or clinical end points between the groups. Interestingly, subgroup analyses suggested that in more severe infarction, defined as greater transmurality, cell therapy conferred a significant benefit in LVEF and LV dimension compared with control.

The Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial is the largest randomised controlled trial in stem cell therapy for cardiac repair to date. The original study that enrolled 204 patients with AMI demonstrated a significantly greater improvement in absolute LVEF in patients treated with BMMNCs compared with control at 4 months. As seen in BOOST, the patients with larger infarcts derived the most benefit. Although not sufficiently powered for the purpose, this was the first large scale clinical endpoint data showing mortality and morbidity benefit conferred by intracoronary administration of stem cells.[20] This was borne out at 2 years with significant reductions in combined clinical end point and increases in LV wall motion when assessed on MRI in the patients who received BMMNCs.[21] The 5-year follow-up data, presented at the American Heart Association (AHA) Scientific Sessions 2011,[22] included 100 patients in each treatment arm. While there was only a trend towards improvement in mortality, there was a significant reduction of the combined end point of death, recurrence of MI and revascularisation conferred by a single intracoronary infusion of cells.

Long-term follow-up data from 100 patients enrolled in the Autologous Stem-cell Transplantation in Acute Myocardial Infarction (ASTAMI) trial showed a significant improvement in exercise capacity in the treated cohort at 3 years, although there was no significant difference in LVEF between treatment and placebo arms.[23] The 5-year follow-up for the 'BALANCE' study (Clinical Benefit and Long-Term Outcome After Intracoronary Autologous Bone Marrow Cell Transplantation in Patients With Acute Myocardial Infarction) showed significant and sustained improvement in LV function and reduction in mortality in 62 treated patients compared with 62 control patients. Although this suggests a significant mortality benefit, it is noted that this study was non-randomised.[24] Another large trial (HEBE) consisting of 200 patients has also been published recently[25] showing no significant improvement in LV function in BMMNC treated patients compared with placebo up to 4 months; however, the long-term effects of cell therapy in this study are yet to be reported.

The majority of these studies are in the context of cell administration 5-8 days following AMI. There is still a need to define the optimal time point for cell transfer relative to ischaemic insult. It is conceivable that the improvement in LV function and outcome seen inconsistently between trials may be dependent on the timing of cell transfer as the postinfarct myocardium will have a changing inflammatory milieu. The later time point of 2-3 weeks post-AMI is addressed by the recent LateTIME study.[26] Here, the authors found that in 87 patients randomised to either BMMNCs or control, BMMNC treatment at the given time point did not improve either global LVEF or regional wall motion at 6 months. Although the likelihood is that day 5-7 is the optimal time for delivery of cell therapy post-AMI, not all time points have been investigated. The ongoing trials TIME[27] and SWISS-AMI[28] aim to evaluate the timing of injection further. As yet, the only time point that has not been considered is the very early phase (<12 h post- revascularisation). The REGENERATE-AMI clinical trial (EUDRACT 2007-002144-16) in which BMMNCs are transferred approximately 6 h post-PCI is over halfway through recruitment and will report in 2013.

There is now a need to better define those patients who will benefit from cell therapy. The results of the 5-year follow-up from the BOOST and REPAIR-AMI trials suggest that if ejection fraction is used as a surrogate end point, while the overall effect may be modest for all-comers, subgroups with a large functional deficit at baseline do experience clinically meaningful increments in LVEF. This is further substantiated by the FINCELL substudy[29] in which 78 patients received either BMMNCs or placebo post-thrombolysis and PCI for AMI. Here, a significantly greater BMMNC associated improvement in LV function was observed in patients with baseline LVEF below the median for the group.

Despite the heterogeneity of trial results described, the largest meta-analysis to date comprising 1765 patients and 33 randomised controlled trials demonstrates a modest but significant improvement in LVEF of 2.87% in short-term follow-up, with sustained LVEF improvement of 3.75% after follow-up over 1 year[16] suggesting that adjunctive stem cell treatment in AMI offers an improvement over conventional therapy. These effects while modest are comparable with those seen in landmark studies of primary angioplasty, ACE inhibitors and β-blockers[30] and suggest that a similar additional mortality benefit may be achieved. The majority of trials in this field to date use LVEF as a surrogate clinical end point with little understanding of how this parameter relates to outcome.

Recently, two trials of BMMNCs in AMI have been published attempting to explore alternative surrogate end points. The aim of the 'Bone Marrow in Acute Myocardial Infarction (BONAMI)' was to assess the effect on myocardial variability at 3 months recruiting 101 patients with poor LV function post- AMI to receive BMMNCs or placebo. Myocardial viability was significantly improved in the treated group compared with control.[31] In another trial,[32] LVEF was assessed alongside myocardial perfusion in a similar patient cohort up to 12 months. A small improvement in myocardial perfusion was observed in the BMMNC group compared with control; there was however a significantly lower incidence of combined major adverse cardiac events in the treatment group, highlighting again an ill-defined relationship between potential surrogate markers and hard clinical outcome measures.

One of the most important developments to date is the move from phase II to phase III clinical trials. The majority of the current clinical trials have been designed to assess safety and feasibility only, and being underpowered to assess efficacy of the technology use surrogate markers such as LVEF to assess activity. In order to address this issue, the EU funding programme recently awarded a consortium composed of 17 clinical centres across Europe €6 million to design and conduct the definitive outcome study of BMMNC in AMI (BAMI; http://www.bami-fp7.eu). BAMI will enrol 3000 patients with the primary end point as all-cause mortality making it one of the most exciting developments in the field for several years. The study will be reported in 5 years.

Cell therapy for chronic LV disease

The STAR-heart study is the largest reported experience of BMMNCs in ischaemic heart failure and reported its 5-year follow-up data in 2010.[33] The non-randomised study originally recruited 391 patients with an LVEF of 35% or less who were offered intracoronary administration of autologous BMMNCs. In all, 191 patients received cell therapy and 200 patients received best medical treatment alone. At 5-year follow-up, there were significant improvements in LVEF, contractility, oxygen uptake and exercise tolerance in patients treated with BMMNCs associated with perhaps more interestingly a significantly lower death rate than the control group. This requires confirmation in a double-blinded randomised study. The FOCUS-HF trial[34] is a randomised controlled trial of 30 patients designed to evaluate the effects of transendocardial delivery of BMMNCs in patients with chronic ischaemic heart failure with no option for further revascularisation. At 6 months, although there was no difference in LVEF between the treated and placebo groups, 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. Another recent study[35] assessed the effect of cell therapy as an adjunct to bypass surgery (coronary artery bypass graft (CABG)) in patients with ischaemic heart failure undergoing CABG. An impressive increase in LVEF and reduction in LV dimensions in the BMMNC group were reported at 6-month follow-up.

Long-term data from the first randomised controlled trial of BMMNCs in dilated cardiomyopathy (Autologous Bone marrow Cells in Dilated cardiomyopathy (ABCD) trial) were reported in 2010.[36] In the 41 patients followed to 3 years, there was a significant improvement in LVEF in the treatment group, greater in patients with the New York Heart Association (NYHA) class 3 symptoms compared with NYHA class 4 suggesting improvement in patients was greater in those with less severely damaged myocardium. There was also an associated symptomatic improvement but no mortality benefit was shown. Trials of BMMNCs in non-ischaemic cardiomyopathy are ongoing.

Translation of other cell types into the clinical setting

Another major development in the last 2 years has been the move towards clinical translation of different cell populations and a search for the optimal cell type for cardiac repair with a number of first-in-human trials.

Circulating/mobilised haemopoietic stem cells identified most commonly by markers CD34 and CD133 have been investigated as potential candidate populations in cardiac repair. These cell populations can either be fractionated from BMMNC or mobilised into the circulation using pharmacological agents such as Granulocyte colony stimulating factor (G-CSF). CD34 cells contain more endothelial lineage determined cells and have been previously evaluated in both AMI and refractory angina. The Autologous Cellular Therapy CD34 in Chronic Myocardial Ischemia (ACT-CMI) investigators have recently reported on a large phase II trial evaluating intramyocardial injection of low and high dose autologous peripherally mobilised CD34 cell therapy against placebo in 167 patients with refractory angina. There was found to be a significant improvement in angina frequency and exercise tolerance in the low dose group compared with placebo at 6 and 12 months. There was also an increased mortality in the placebo arm.[37] In contrast, Chih et al report that despite mobilisation of CD34 and CD34/CD133 cells using G-CSF, no improvement in angina or myocardial perfusion was observed in patients with chronic Ischaemic heart disease (IHD)[38] Again, this discrepancy in the findings from these studies suggests that careful consideration to the method of delivery should be given and that intramyocardial delivery may be more effective in this type of patients.

MSCs are able to release a large range of cardioprotective paracrine factors and transdifferentiate into a number of cell types that are involved in cardiac repair and are therefore increasingly being used in clinical trials which have shown promising results. Another advantage of MSCs is their logistical ease of access via bone marrow and adipose tissue.

The 6 month results of the first-in-human randomised controlled 14 patient trial of autologous adipose tissue derived stem and regenerative cells (ADRCs) for AMI (the Adipose-derived stem cells in the treatment of patients with ST-elevation myocardial Infarction (APOLLO) trial) have recently been reported.[39] All patients received either cell therapy or placebo within 24 h of primary PCI. These were first MI patients with an LVEF between 35% and 50%. At 6 months, there was a significant improvement in myocardial scar formation and perfusion defect, near significant reduction in infarct size and improvement in estimated ejection fraction with cell therapy compared with control, and the treatment proved safe. The 18 month data were presented at the 2011 International Symposium on Stem Cell Therapy & Cardiovascular Innovation and showed sustained benefits. The next step, a larger study called ADVANCE, enrolling 375 patients will give greater statistical power. Eighteen month results for a similar first-inhuman trial of ARDCs for ischaemic heart failure, PRECISE, although not yet published, have been presented at the AHA Scientific Sessions 2010.[40] Here, 27 patients were randomised to receive transendocardial ADRCs or placebo. Results at 6 months showed a significant reduction in infarct size in the treatment group relative to the controls but with no difference in LVEF. Out to 18 months, cell therapy was found to be safe with no difference in adverse outcomes between the two groups and found to significantly improve both NYHA and Canadian cardiovascular society (CCS) class symptoms, metabolic equivalents and peak oxygen consumption, in the treatment group.

Allogeneic as opposed to autologous MSCs have also recently been evaluated as a potential novel therapeutic strategy allowing for 'off-the-shelf' logistical ease. MSCs are able to evade immune detection meaning immunosuppression is not required for these patients. The first-in-human phase I randomised controlled study comparing allogeneic MSCs with placebo in the setting of first AMI and LV dysfunction enrolled 53 patients.[41] Importantly, the study demonstrated no difference in adverse events, rehospitalisation or arrhythmia between the groups. At 18 months, the treatment group conferred significant improvement in LVEF relative to controls. The preliminary results of a phase II randomised controlled trial assessing allogeneic MSCs in the setting of ischaemic heart failure were presented at the AHA Scientific Sessions 2011.[22] The study consisted of 60 patients with a 12 month follow-up period and confirmed safety of the technology. While there was no difference in LVEF between the two groups, there was a significantly lower incidence of major adverse cardiac events, mortality and symptoms in the treated group supporting the concept of LVEF not being a useful surrogate marker for outcome.

The attractive opportunity to exploit cardiac stem cells (CSC) which are capable of regrowing healthy heart tissue was realised with the discovery that the adult heart contains its own reservoir of progenitor cells. There are two main CSC populations that have been described, the c-kit+ population and cardio- sphere-derived cells, which are a natural mix of heart derived cell subpopulations including c-kit+/CD90- and cardiac MSCs c-kit-/CD90. Although it is uncertain as to whether these will prove advantageous over other stem cell types, particularly if they act in a paracrine manner, both populations have been studied in the clinical setting.

The recently published SCIPIO trial (Cardiac stem cells in patients with ischaemic cardiomyopathy) is a first-in-human phase I trial assessing the value of c-kit+ CSCs in ischaemic heart failure post-CABG.[42] Here, autologous atrial appendage c-kit+ cells are isolated and expanded at the time of CABG and re-infused 3-4 months after surgery. Importantly, there was no difference in adverse event rate between treatment and control arms. At 8 months, there was a significant improvement in infarct size and LVEF in treated patients. The CADUCEUS trial (cardiosphere-derived autologous stem cells to reverse ventricular dysfunction) assessed the impact of intracoronary infusion of autologous cardiosphere-derived cells harvested from endomyocardial biopsies in patients 2-3 months post-AMI in a phase I clinical trial.[43] Here, LVEF was significantly improved at 12 months compared with controls and there was a major reduction in scar mass on Cardiac magnetic resonance imaging (CMR) in the treated but not the control group. There was no difference in adverse outcome between the groups. Importantly, this is one of the first trials of cell therapy to suggest that the benefits seen in relation to myocardial repair are explained by a regenerative process. The results of a phase II trial will be eagerly awaited.

Although the ultimate goal of cell therapy is to restore cardiac function and thereby improve quality of life and survival, the mechanism by which this is achieved using cell therapy continues to remain a topic of debate depending on the cell type used. This area of research has nonetheless led to a better understanding of how cells can in vitro be made to differentiate into a phenotype that may improve cardiac repair. The first results of this approach in humans have recently been published. In the C-Cure trial, the investigators have driven the differentiation of BMMNCs into lineage-specific cardiac progenitor cells using cardiogenesis proteins before cell transfer via the trans-endocardial route[44] to 45 patients with ischaemic heart failure. At 6 month follow-up, there was significant improvement in LVEF and reduction of LV volumes as well as significant symptomatic improvement evidenced by the 6 min walk test in the treated group compared with the control group. There were no significant differences in adverse outcome. The second phase of this trial is ongoing.

Summary

Cell therapy research offers the prospect of a completely new therapeutic approach in cardiology. The last 2 years has seen a systematic move from phase I to phase II clinical trials using established cell types together with the emergence of new cell types in phase I studies that have only become feasible due to the research that has been driven by the early translation into humans. For the pragmatic approach of bone marrow derived cell therapy, recent meta-analysis again confirms the potential for benefit and this will now be addressed in a phase III outcome study that will also standardise the technique of cell processing and administration. Other cell types will need to follow a similar path of investigation and no doubt the trials of bone marrow derived cells will set the standards by which different cell types and techniques will be judged.

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