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Clinical Trials Using Cell-based Therapy in Ischemic Heart Diseases - A Decade's Efforts

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Introduction

The primary goal in treating ischemic heart disease is stimulating angiogenesis. Investigators have tried mechanical strategies [1-4], and employing pharmacologic strategies using heparin [5,6] and growth factors [7-10]. In the late 1990s, cell-based therapy was introduced as a method to stimulate therapeutic angiogenesis for ischemic heart disease [11,12]. Over the past decade, cell-based therapy for ischemic heart disease has rapidly progressed and became a dynamic research field [13]. Using either embryonic or adult stem cells, two classical concepts, have been challenged by cell-based therapy. First, the concept of vasculogenesis was challenged. This previously referred to a process that occurred only in the embryo, where the vascular system develops from mesodermal precursor cells called angioblasts which invade the different embryonic organs and assemble in situ to form the primary capillary plexus [14]. Now many investigators believe that in adults, bone marrow–derived stem cells or endothelial progenitor cells can be recruited to and incorporated into tissues undergoing neovascularization [11,12,15-30]. Second, cardiac myocytes originally were considered to be terminally differentiated cells that cannot be regenerated in adulthood. However, recent studies have shown that a limited number of cardiomyocytes may be regenerated by locally sited or recruited circulating stem cells [31-34]. Therefore, stem cells, which include hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), mesenchymal stem cells/stromal stem cells (MSCs), myoblasts, and undifferentiated side population cells, have been used as an alternative therapeutic strategy for ischemic cardiovascular diseases that cannot be treated by routine interventional approaches [13,15-30,35-41]. Theoretically, embryonic stem cells have more potential to differentiate into cardiomyocytes [42]; however, most clinical trials are limited to autologous adult stem cell transplant due to the ease of handling and ethical restrictions. This brief review is therefore focused on the status and progress of clinical trials utilizing these cells.

Intracoronary Infusion of Autologous Bone Marrow-Derived Cells

In the Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) Trial, Assmus et al. first reported cell-based therapy for 20 acute myocardial infarction (AMI) patients in 2002 [15]. In this study, the authors performed intracoronary infusion of autologous bone marrow–derived mononuclear cells (n=9) or circulating blood-derived progenitor cells (n=11) 4 to 5 days after AMI. The circulating blood-derived progenitor cells were expanded ex vivo for 3 days before injection. The bone marrow–derived cells were extracted on the same day as injection without expansion. At 4 months following cell injection, patients' cardiac function was improved compared with 11 matched controls. The authors also reported a post-infarction remodeling outcome using serial contrast-enhanced magnetic resonance imaging (MRI) [16]. A total of 28 patients with reperfused AMI who received bone marrow-derived cells or circulating blood progenitor cells were analyzed. They found that intra-coronary infusion of adult progenitor cells in patients with AMI beneficially impacts the post-infarction remodeling processes. The migratory capacity of the infused cells is a major determinant of infarct remodeling, suggesting a causal effect of progenitor cell therapy on regeneration enhancement [16]. In 2011, the 5-year follow-up data for TOPCARE-AMI provided reassurance with the long-term safety of intracoronary cell therapy, as all of the 5-year follow-up patients (n=55) didn't show any signs of intramyocarical calcification or tumors at 5 years. The 5-year follow-up data also showed promising results on left ventricular (LV) function. Serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) remained reduced at the 5-year follow up. Also, MRI subgroup (n=31) had improvement of their LV ejection fraction (from 46 +/-10% at baseline to 57 +/- 10% at 5 years, $p<0.001$) [17].

Assmus et al. also performed a clinical study investigating the use of bone marrow–derived progenitor cells (BMCs) for chronic postinfarction heart failure patients. In this study, 121 patients with chronic ischemic heart disease were treated with BMCs. 3 months after injection if BMCs, NT-proBNP and N-terminal pro-atrial natriuretic peptide (NT-proANP) serum levels were reduced. They also found that infusion of BMCs with a high functional capacity was associated with a lower mortality during the extended clinical follow-up (577+/-442 days) [18].

Strauer et al. conducted a study to test the effect of autologous BMC injections on myocardial repair and regeneration. The authors first reported the data with 10 AMI patients who received BMCs by intracoronary injection and compared with 10 compatible patients treated with standard therapy alone. At 3 months following cell therapy, they found that the infarct region had decreased significantly and wall motion also significantly improved [19]. Recently, the same group reported another study using the same cell therapy technique on 18 patients with chronic myocardial infarctions (MI) (range of 5 months to 8.5 years old infarct) for their effects on myocardial regeneration. At 3 months, the patients with cell therapy showed that the infarct size was reduced by 30% and global left ventricular ejection fraction and infarction wall movement velocity increased significantly, whereas in the control group no significant changes were observed. The authors also found that following BMC transplantation there were improvements in maximum oxygen uptake and regional F-fluor-

desoxyglucose uptake into infarct tissue suggesting a regeneration of myocardium after infarction [20].

The initial Bone Marrow Transfer to Enhance ST-elevation Infarct Regeneration (BOOST) trial was reported by Meyer et al. [21]. This study showed significant improvements in global and regional left ventricular systolic function. However, the 5-year follow-up from this trial showed that a single intracoronary infusion of BMCs did not promote a sustained improvement in left ventricular ejection fraction in patients with ST-elevation myocardial infarctions [22].

Long term outcomes of the HEBE trial were completed in 2014. The HEBE study was a multicenter trial that randomized 200 patients after their first large acute myocardial infarction. Patients were treated with a percutaneous coronary intervention and either intracoronary infusion of bone marrow mononuclear cells (BMMC), peripherial blood mononuclear cells (PBMC), or standard therapy. Of the three groups, the BMMC group showed less increase in LV end-diastolic volume (LVEDV) (3.5 ± 16.9 mL/m^2) versus the control group (11.2 ± 19.8 mL/m^2, p=0.03) and a trend for decrease in LV end systolic volume (-1.8 ± 15.0 mL/m^2) versus the control (3.0 ± 16.3 mL/m^2, p=0.07). There was no difference in LVEDV between the PBMC group and the control. The composite endpoint of death or recurrent myocardial infarction was higher in the PBMC group compared with controls (14 patients vs 3 patients, p=0.008); there was no difference between the BMMC group and controls (2 vs 3 patients, p=0.67) [43].

Catheter-based Transendocardial Cell Injection

Perin et al. reported their results using a NOGA® catheter technique to transendocardially inject autologous BMSC in severe chronic ischemic heart failure patients. In 14 patients, who received cell injection, there was significant functional improvement compared with 7 controls. A phase 2 randomized, multi-center, double-blind, placebo- controlled trial of symptomatic patients (New York Heart Association classification II-III or Canadian Cardiovascular Society classification II-IV) with a LV ejection of 45% or less, a perfusion defect by single-photon emission tomography (SPECT), coronary artery disease that was not amenable to revascularization, and were on maximal medical therapy concluded in 2011 [23]. This study also utilized transcardial delivery of BMSC via the NOGA catheter technique. 92 patients were randomized (n=61 in BMC group and n=31 in placebo group). The results showed that BMSC compared with the placebo did not improve LVESV, maximal oxygen consumption, or reversibility on SPECT [44].

Similar methods also were reported by Fuchs et al. in Washington Hospital Center in 10 no-option patients with advanced coronary artery disease (CAD). The authors first studied a porcine ischemic model to test the effect of freshly extracted autologous bone marrow on myocardial blood perfusion. Improved collateral flow and contractility in a treated group of animals was demonstrated [24]. Subsequently, in a pilot clinical study, 10 patients with advanced CAD received autologous bone marrow direct myocardial injections that showed a significant improvement in the Canadian Cardiovascular Society angina score and decrease in stress-induced ischemia occurring within the injected territories [25].

The TAC-HFT is a phase 1 and 2 randomized, blinded, placebo-controlled study involving 65 patients with ischemic cardiomyopathy that demonstrated the safety of transendocardial stem cell injection (TESI) with autologous MSCs and BMCs. Over the course of a year, the patients' heart failure score improved with MSCs (−6.3; 95% CI, −15.0 to 2.4; repeated measures of variance, P=.02) and BMCs (−8.2; 95% CI, −17.4 to 0.97; P=.005). The heart failure score results didn't improve with the placebo. Regional myocardial function as peak Eulerian circumferential strain at the site of the injection improved and infarct size as a percentage of LV mass was reduced in the MSC group; however, the results were unchanged in the BMC group and the placebo group [45].

A biorespostory evaluation from the CCTRN TIME trial identified BMCs characteristics that were associated with a reduction in infarct size after ST-segment-elevation-myocardial infarction (STEMI) in 101 patients. This study looked at the change in infarct size between baseline (3 days after percutaneous coronary intervention (PCI) and 6-month follow-up with cardiac MRI. At 6 months, 74.3% of patients had a reduction in the infarct size (mean change, -21.0±17.6%). A greater reduction in infract size was seen in patients with a larger percentage of CD31(+) BMCs (P=0.046) and in patients with faster BMC growth rates. This study was able to highlight the importance of endothelial precursor activity in regenerating infarcted myocardium. The study also advocated that the most important factor in myocardial repair was baseline BMC characteristics [46].

Intracoronary Injection of Extra-Vivo Expanded BMSC

Chen et al. were the first group to use autologous ex vivo expanded bone marrow–derived mesenchymal stem cells in patients with AMI. In their study, a total of 69 patients who received PCI 12 hours after AMI were chosen randomly for either cell injection (n=34) or placebo (n=35). The bone marrow–derived mononuclear cells were cultured in vitro for 10 days, and then patients underwent intracoronary injection of the fibroblast-like mesenchymal stem cells. Patients who received mononuclear stem cell injection showed significant improvement in LV function at 3 to 6 months of follow-up [26].

Mobilized Peripheral Blood Mononuclear Cell Studies

Kang et al. reported a mobilized PBMC study for AMI patients after coronary stenting. A total of 27 patients with AMI who underwent PCI 48 hours later were studied. Ten patients received intracoronary injection of mobilized [granulocyte colony-stimulation factor (G-CSF) 10 μg/kg for 4 days] PBMCs. Ten patients received injection of G-CSF alone, and 7 patients served as controls with neither PBMC nor G-CSF. At 6 months, the cell infusion group showed improvement in LV function compared with the other two groups [27].

A subsequent randomized placebo-controlled trial, Regenerate Vital Myocardium by Vigorous Activation of Bone Marrow Stem Cells (REVIVAL-2), reported by Zohlnhofer et al. [28] showed that stem cells mobilized by G-CSF therapy did not improve infarct size, left ventricular function, or coronary restenosis in patients with AMI who had successful mechanical reperfusion.

Autologous Myobast Studies

The first reported use of autologously transplanted skeletal myoblasts to improve ventricular function in animal models of heart failure was discussed by Taylor et al. [35]. This has been a widely discussed topic in the field of cell-based therapy for the last decade. However, Menashe et al. performed a multicenter, randomized placebo-controlled clinical study of autologous myoblast transplantation in patients with LV dysfunction, MI, and indication for coronary surgery. Patients (n=97) were randomized to receive

expanded cells from a skeletal muscle biopsy (400 million or 800 million; n=33 and n=34, respectively) or a placebo (n=30) injected around the scarred myocardium. The treatment groups did not show improvement in regional or global LV function over control group. The high-dose cell group did demonstrate a significant decrease in LV volumes over the placebo group. This study failed to prove any significant change in echocardiographic heart function in patients with LV dysfunction who were treated with myoblast injections combined with coronary surgery [36].

The SEISMIC trial was a prospective, randomized study to evaluate percutaneous myoblast implantation in heart failure patients with implanted cardioverter-defibrillators (ICD). Patients (n=40) were randomized 2:1 with autologous skeletal myoblast therapy in the treatment arm (n=26) vs medical treatment in the control arm (n=14). At 6 months, the six-minute walk test distance improved by 60.3 ± 54.1 meters in the treated group versus no improvement in the control group (0.4 ± 185.7 meters; P=ns). At 6 months, the treatment arm did not show any improvement global LVEF in the by the multigated acquisition scan (MUGA). This study did not show any significant benefit to global LVEF at 6 months [47].

While multiple studies have failed to prove any statistically significant improvement in LV function with cardiac myoblasts, Roell et al. discovered that the transplantation of embryonic cardiomyocytes (ECMs) in myocardial infarcts has a protective effect against ventricular tachycardia (VT) in a mouse model. The protection against VT involves the gap-junction protein connexin 43, of cardiomyocytes, which can augment intracellular coupling. They concluded that transplantation of connexin 43 expressing myocytes has the ability to reduce the incidence of VT [48].

Direct Epimyocardial Cell Transplantation

Patel et al. recently reported direct myocardial injection of autologous bone marrow–derived stem cells in 10 patients who underwent bypass surgery. Six months later, the cell injection patients showed improvement in left ventricular function compared with 10 patients who received bypass surgery alone. No side effects were found with this direct stem cell injection [29].

Ascheim et al. recently investigated whether allogeneic mesenchymal precursor cells (MPCs) injected during left ventricular assist device (LVAD) implantation would contribute to recovery of the myocardium. The study was a multi-center, double-blind, controlled trial involving 30 patients randomized 2:1. The patients had an intramyocardial injection of 25 million MPCs in the treatment arm or medium in the control arm during LVAD implantation. The patients were followed to transplant or up to 12 months after randomization. Successful LVAD weaning was achieved in 50% of MPC and 20% of control patients at 90 days (P=0.24). The mean left ventricular ejection fraction after being weaned off of the LVADs was 24.0% (MPC=10) vs 22.5% (P=0.56). At 12 months, 30% of MPC patients and 40% of control patients were successfully temporarily weaned from LVAD support (P=0.69). At 12 months there were 6 deaths (30%) in MPC patients. Also, donor-specific HLA sensitization developed in 2 MPC and 3 control patients. All patients had resolution of donor-specific HLA sensitization by 12 months [49].

Allogeneic Mesenchymal Stem Cell Therapy

Osiris Therapeutics Inc has completed its first allogeneic hMSC cell line clinical trial reported by Hare et al. In this study, hMSCs, developed by Osiris Therapeutics Inc more than 10 years ago, were administered intravenously to patients (n=53) with an AMI at a dose range of 0.5, 1.6, and 5 million cells/kg. They found that the allogeneic stem cell therapy was safe demonstrated a significant reduction in episodes of ventricular tachycardia (p=0.025), a decrease in global symptom score (p=0.027) and improvement in left ventricular ejection fraction in a subset of anterior MI patients. The study suggested the potential usage of allogeneic cell therapy in the future and importantly demonstrated no signs of rejection of transplanted cells [30].

Adipose-derived Regenerative Cells

The PRECISE trial examined adipose-derived regenerative cells (ADRCs), which can be isolated from liposuction aspirates. This option is appealing because autologous MSCs require ex vivo culture and expansion, however, ADRCs can be obtained after liposuction and prepared for immediate autologous transplantation. The efficacy was evaluated with echocardiography and single-photon emission computed tomography, metabolic equivalents, maximal oxygen consumption (MVO2), and cardiac MRI [23]. Patients were in the ADRC arm and 6 patients in the control arm. Metabolic equivalents and MVO2 values were unchanged over 18 months in treatment arm, but decreased in the control arm. The treatment arm also had improvements in the total left ventricular mass by MRI and wall motion score index. Also, single photon emission computed tomography showed a reduction in inducible ischemia in ADRC-treated patients [50].

Potential for Deleterious Effects

The biologic activities of most of the angiogenesis agents currently being tested clinically are very potent, and it is likely that the same activities that lead to a therapeutic effect could also cause unwanted side effects. It is probable that some side effects, as a result of the cellular effects of these agents, will inevitably occur. If this concept is true, then the critical questions that need to be addressed in large clinical trials are whether the incidence of these risks is sufficiently low enough and if these risks will be outweighed by the therapeutic benefits.

Among the side effects that might occur by cell transplantation is the development of new blood vessels in non-targeted tissues, a complication that would be particularly devastating if it were to occur. In cell-based therapy, most of the clinical trials so far are using non ex vivo expanded or short-time expanded (4 to 5 days) cells. In animal studies, stem cells can potentially transform during in vitro expansion. These transformed cells can create tumors in nude mice [37]. Similar incidents occasionally occur in adult human bone marrow–derived mesenchymal stem cells. While it is still not clear which cell type is best for patients with a MI; however, if it is decided to use ex vivo expanded cells, one has to be certain that these cells are not tumorigenic. It is absolutely necessary to test these cells for tumorigenic potential in nude mice and to perform a karyotyping test before injecting them into patients.

The use of ADRCs is a potential source of multipotent stem cells that can provide growth factors in addition to cytokines for myocardial tissue repair while eliminating tumorigenic potential. However, further research is needed to prove the efficacy of this treatment modality [50].

Comparison of Current Therapeutic Strategy and Future Prospectus

Beneficial effects or functional improvements have been reported using these cell-based therapies except in the large scale MAGIC trial [36], possibly due to the limited paracrine effects by this special cell-type and origin. The Osiris follow-up study, looking at a large scale of patients, showed no improvement in left heart function [30]. Some researchers speculate this is because the cells were delivered intravenously, since most of the cells were found trapped inside the lungs. Experimental studies showed that the cell-types described above are not capable to differentiate into a beating myocyte, so the functional improvements are due to the paracrine effects caused by the delivered stem cells.

As for the issues regarding which cell type is better, this is still a controversial topic. The majority of un-selected and non-expanded bone marrow derived mononuclear cells are hematopoietic lineage cells. The beneficial effects created by these cells are limited and definitely entail less paracrine effects compared with MSCs or other selected stem cells. So far, bone marrow derived MSCs are still the most popular cell type used by most investigators. The optimal delivery technique or route for the cells is another highly debated topic in the field. Intracoronary infusion was the first method used in patients with ischemic coronary heart diseases. The problem encountered during this practice entails the need to block the blood flow during cell infusion and for a few seconds thereafter. This may cause ischemia of the surrounding myocardium. Additionally, the infused cells will be flushed out after reperfusion. The advantage of intravenous delivery is that it is non-invasive, however, the major disadvantage of this route is the finding that cells become trapped in the lungs instead of the heart. Investigators have also tried to deliver cells intramyocardially using special injecting devices, or by direct epimyocardial injection during open heart surgery. This approach partially solves the issue of cells homing to the target tissue. However, large amounts of cells disappear following injection into the myocardium. Therefore, polysaccharide-based strategies are studied in an effort to create a friendly environment to increase the survival and retention of cells after delivery. Our lab has tried co-transplanting regulatory T cells with MSCs in a large animal model of myocardial ischemia and shown beneficial effects on MSC survival and self-renewing [51]. The results from this study may help with future clinical applications of cell-based therapy.

Induced pluripotent stem cells (iPSCs) have been successfully generated in murine, human, and several other species over the past decade by both scientists in Japan and the United States. These iPSCs have become exciting tools for understanding the mechanisms of diseases and for potentially treating diseases through cell replacement therapy. We recently used two lines of iPSCs one from our own lab and the other from a different lab to study their ability to stimulate angiogenesis in a porcine model of chronic myocardial ischemia. We found that allogeneically transplanted pig iPSCs could survive for at least three months in ischemic regions of the heart in immunocompetent hosts. The iPSC in vivo proliferation was limited to the first two months post transplantation. These cells were able to stimulate angiogenesis and, thus, might have beneficial effects on the injured myocardium and global cardiac function. However, these iPSCs did not automatically differentiate into myocytes in an ischemic environment [52]. Therefore, in order to apply this new technology for future clinical use, more research needs to be done to stabilize the myocyte differentiation rate and purity of the cells after differentiation.

Summary

While the field of regenerative medicine for the prevention and interventional treatment of ischemic cardiovascular disease has drastically advanced over the past decade, there is still much progress to be made. There is currently no consensus regarding the most advantageous method of delivery: intravenous, intracoronary, catheter-based transendocardial, or epimyocardial. There has also been no consensus with the best type of cells to use: ADRCs, BMMCs, BMSCs, hMSCs, MPCs, or PBMCs. While there is currently much debate over the aforementioned methods of delivery and cell types, there is still a considerable amount of research that remains to determine which therapies correlate with the best clinical outcomes. Decades ago there was no known therapy to regenerate ischemic heart muscle, now it is a reality. With the rapid advancement in the field of cell-based therapies for ischemic cardiovascular disease, it will be fascinating to see what innovations the next decade will bring.

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