Review

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A Long Road for Stem Cells to Cure Sick Hearts: Update on Recent Clinical Trials

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The contribution of stem cells to cure damaged hearts has finally been unraveled. A large number of preclinical and clinical studies have showed beneficial outcomes after myocardial infarction. In this review, the current understanding of stem cell therapy in preclinical and clinical experiences is summarized. Stem cells from bone marrow have shown a potential to improve cardiac performance after myocardial infarction in animal and early clinical studies. Clinical trials from all over the world have provided safety assessments of stem cell therapy with marginal improvement of clinical outcomes. Thus, further investigations should be encouraged to resolve the discrepancies between studies, clinical issues, and unclear translational findings. This review provides information and commentary on key trials for stem cell-based treatment of cardiovascular disease. **(Korean Circ J 2012;42:71-79)**

KEY WORDS: Stem cells; Myocardial infarction; Animal experimentation; Clinical trial; Peer review, research.

Introduction

According to a World Health Organization (WHO) report, cardiovascular diseases (CVDs) are the number one cause of death globally. It was estimated that 17.3 million people died from CVDs in 2008, representing 30% of all global deaths. In addition, it is predicted that almost 23.6 million people will die from CVDs by 2030 (WHO, 2011). The most important risk factors of CVDs are unhealthy diet, physical inactivity, smoking, and harmful use of alcohol. The effects of unhealthy diet and physical inactivity may show up in individuals as raised blood pressure, raised blood glucose, raised blood lipids, and overweight and obesity. These are called metabolic risk factors.

Rapid reperfusion of the culprit vessel for salvaging ischemic myocardium and optimal medications reduce complications and improve survival rate. Although many drugs and medical devices have been developed, the incidence of CVDs remains high. More efficacious therapeutic modalities need to be explored by medical researchers. Since the discovery of stem cells, a significant amount of research and development has emerged to be clinically applied for various incurable diseases including CVDs.

The human heart is a dynamic organ. Traditionally, the myocardium has been considered as terminally differentiated; however, there is growing evidence that cardiomyocytes are able to become proliferative when they face substantial damage such as myocardial infarction or heart failure.[1)2)] In addition to intrinsic repair mechanisms, progenitor/stem cell plasticity has emerged as one of the ways to be regenerated.[3)]

Stem cells are undifferentiated pluripotent multilineage cells with the ability to renew themselves. The sources of stem cells include the embryo, fetus, and various parts of adult tissues. Stem cells or progenitor cells are classified according to their characteristics in Table 1.

Many clinical trials showed excellent safety and feasibility of adult stem cells, but the efficacy of stem cell therapy is not satisfactory to improve cardiac function substantially.

The basic mechanisms of stem cell action on the injured myocardium will not be discussed here. We will focus instead on the current status of preclinical/clinical studies regarding therapeutic opportunities.

In this review, we summarize recent results of preclinical/clinical trials that have evaluated the safety, feasibility, and efficacy of cell therapy in heart disease.

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Table 1. Major cell types with potential for cardiac cell therapy

Cell type	Source	Advantages	Limitations
Cardiac stem cells	Allogenic fetal, neonatal, or adult heart	Recognition of myocardial growth factors and recruitment to myocardium are likely faster and more efficient than other cell types *In vivo* electrical coupling of transplanted cells to existing myocardium has been demonstrated	Poor cell growth *in vitro* Transplanted cells are very sensitive to ischemic insult and apoptotic cell death Availability from either fetal (F), neonatal (N), or adult sources is low at present; likely immune rejection; F and N cells pose ethical difficulties
Skeletal myoblast	Autologous skeletal muscle biopsy	Cells proliferate *in vitro* (allowing for autologous transplant) Ischemia resistant Transplanted myoblasts can differentiate into slow-twitch myocytes (similar to cardiomyocytes) enabling cellular cardiomyoplasty Reduces progressive ventricular dilatation and improves cardiac function Can use adult cells	Likely do not develop new cardiomyocytes *in vivo* Electrical coupling to surrounding myocardial cells is unclear Long-term stability of differentiated phenotype unknown
Adult bone marrow stem cells	Autologous bone marrow stromal cells (mesenchymal); bone marrow (endothelial progenitor cells)	Pluripotent stem cells can develop into cardiomyocytes Stem cells are easy to isolate and grow well in culture Neovascularization can occur at the site of myocardial scar reducing ischemia Transdifferentiation of cells into cardiomyocytes *in vivo* has been shown Can be derived from autologous source; no immune-suppression treatment Can improve myocardial contractile function	New program of cell differentiation is required Efficiency of the differentiation into adult cardiomyocytes appears limited Signaling, stability, and regulation of differentiation unknown
Embryonic stem cells	Allogenic blastocyst (inner mass)	Easy propagation and well-defined cardiomyocyte differentiation process *In vivo* electrical coupling of transplanted cells to existing myocardial cells Pluripotent cells	Potential for tumor formation and immune rejection (allogenic) Incomplete response to physiological stimuli Legal and ethical issues Donor availability

Marin-Garcia M. Heart failure: bench to bedside. New York: Springer; 2010

Walking With Animal Study

Direct or indirect transplantation of adult stem cells to damaged hearts is emerging as an innovative strategy to ameliorate cardiac remodeling and dysfunction after acute myocardial infarction (AMI).

Potential sources of functional cardiomyocytes has been explored and utilized for cell therapy to replace injured cardiomyocytes. Stem cells are characterized by their ability to self-renew, clone, and differentiate into multiple tissues. Adult stem cells are isolated and characterized from various sources; peripheral blood,[4] bone marrow (BM),[5] adipose tissue,[6] umbilical cord blood,[7] amniotic membrane,[8] and dental pulp.[9]

A large number of animal studies have demonstrated that stem cells could be engrafted and differentiated within the heart.[3][10-12] In preclinical studies, several large-animal species, including swine, sheep, and dogs, have been used to investigate the effects of stem cell therapy in CVDs models. Stem cells can be delivered to the heart by intravenous infusion, direct surgical injection, or catheter-based intracoronary infusion.

Orlic and colleagues first reported the repair of infarct myocardium through transplantation of bone marrow cells (BMCs) in mice.[3]

Progenitors or stem cells with cardiomyogenic potential were studied both *in vitro* and *in vivo*. Experimental data showed the expression of cardiac markers such as cardiac contractile proteins in stem cells in transplanted myocardium. However, they were rarely found.

One of the popular strategies to increase the cardiomyogenesis of stem cells is the stimulation of stem cells with an anticancer drug, 5-azacytidine, which is a nonspecific deoxyribonucleic acid methylation inhibitor. Transient stimulation with 5-azacyticine for one day substantially increased cardiac protein expression in BM-derived mesenchymal stem cells (MSCs) and sca-1-positive adult cardiac stem cells with spontaneous beating on culture system.[13]

To prove functional stem cell therapy, a small animal model has widely been used. Myocardial infarction was experimentally induced by surgical ligation of the coronary artery such as left anterior descending artery in mice or rats, sometimes with reperfusion. Various stem cell types, transplantation route, cell number, and transplantation timing have been studied in these small animal models. Many studies are reported that stem cell therapy is safe, feasible, and promising for the cure of MI. Histological data has revealed that the injected stem cells can survive in ischemic myocardium that participated in neovascularization and cardiomyogenesis. Scar size, cardiac remodeling, fibrosis, and inflammation were much more effectively improved. Cardiac function was also substantially improved after stem cell therapy. Based on these fantastic results of animal studies, many clinical studies were designed and initiated to

Table 2. Summary of results from mesenchymal stem cell therapy cases in the swine model

Study	Cell type/delivery route	MI induction	Time of delivery	Results	F/U	F/U measurement
Shake et al.[36]	Autologous BM-MSC, 10^7 cells/direct injection	60-minute LAD occlusion	2 week	Systolic wall thickening ↑	4 week	Sonomicrometry crystals
Amado et al.[37]	Intramyocardial injections of either allogeneic porcine MSCs (2.0×10^8 cells)	60-minute LAD occlusion	3 day	Diastolic function ↑, mechanoenergetics ↑, EF ↑, EDV ↓		CMR
Lim et al.[16]	Allogeneic BM-MSC, 1×10^7cells, IC	30-minute LAD occlusion	3 day	EF ↑, infarct area ↓, viable myocardium ↑		SPECT
Price et al.[38]	Allogeneic, $3.2\pm0.4\times10^8$ cells, IV (internal jugular vein)	60-minute LAD occlusion	30 minute	EF ↑, hypertrophy ↓	12 week	Echocardiography
Freyman et al.[39]	Allogeneic BM-MSC, 5×10^7 cells, IV, IC, EC	60-minute LAD occlusion	1 5 minute	Engraftment within infarct myocardium ↑: IC>EC>IV Remote organ engraftment: EC<IC, IV	2 week	FISH staining
Feygin et al.[40]	Autologous BM-MSC, 5×10^7 cells, direct intramyocardial injection	LAD ligation after left thoracotomy	Right after MI	Contractile performance ↑, wall stress ↓	12 week	CMR
Schuleri et al.[41]	Allogeneic BM-MSC, intramyocardial injection	60-minute LAD occlusion	3 day	Cardiac performance ↑, infarct size ↓	8 week	CMR
Hashemi et al.[42]	Allogeneic BM-MSC, 2.4×10^7, 2.4×10^8, 4.4×10^8 cells, endomyocardial delivery	60-minute LAD occlusion	3 day	Safe and produced a local but not a functional effect	12 week	CMR
Gyöngyösi et al.[43]	Allogeneic BM-MSC, 7.2×10^6 cells, intramyocardial injection	60-minute LAD occlusion	16 day	The persistence of viable MSC at 10 days after delivery	10 day	CMT, PET-CT
Wolf et al.[44]	Autologous or allogeneic BM-MSC, 1×10^3 to 1×10^6/kg, iv (ear vein)	LAD ligation after lateral thoracotomy	2 day	EF ↑, infarct size ↓	4 week	Echocardiography
Moscoso et al.[45]	5-azacytidine-treated BM-MSC, $31.7\pm11.61\times10^6$, IC, IM, EC	120-minute LAD occlusion	1 month	Engraftment rate: IC<IM, EC	1 month	Postmortem section
Ly et al.[46]	MPC, MSC, MNC, PBMNC, 2×10^7 cells, IC	60-minute LAD occlusion	3-4 day	Retention rate: MSC ↑	1 hour	Near-infrared fluorescence
Schuleri et al.[47]	Autologous BM-MSC, 2×10^7 or 2×10^8, surgical injection	120-minute LAD occlusion	12 week	Regional contractility ↑, infarct size ↓	12 week	CMR
Dubois et al.[48]	Autologous EPC ($34\pm22\times10^6$), allogeneic MSC ($10\pm2\times10^6$), IC	90-minute occlusion of proximal circumflex artery	1 week	EPC: infarct size ↓, vascular density ↑, MSC: EF ↑	7 week	CMR
Ellison et al.[49]	IGF-1 & HGF administration to activate endogenous cardiac stem cells	60-minute LAD occlusion	30 minute	Fibrosis ↓, hypertrophy ↓, infarct size ↓, cardiac function ↑	8 week	CMR

BM: bone marrow, CMR: cardiac magnetic resonance imaging, EDV: end-diastolic volume, EC: endocardial injection, EF: ejection fraction, EPC: endothelial progenitor cells, HGF: hepatocyte growth factor, IC: intracoronary infusion, IGF-1: insulin like growth factor-1, IM: intramyocardial injection, LAD: left anterior descending artery, MNC: mononuclear cells, MPC: multipotent progenitor cells, MSC: mesenchymal stem cells, PBMNC: peripheral blood-derived mononuclear cells, PET-CT: positron emission tomography-computed tomography, SPECT: single-photon emission computed tomography, MI: myocardial infarction, IV: intravenous, FISH: fluorescence *in situ* hybridization, F/U: follow-up

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transfer stem cell therapy to the bedside all over the world.

Various stem cells or progenitor cells have been introduced for cardiac repair in the last few years, although many past and ongoing clinical trials use predominantly adult autologous BM-derived cells. The use of BMCs in CVDs has the advantage that BM can be easily accessed, and isolated cells can be expanded for autologous application.

Experimental studies of cell priming revealed that it improved cell survival, retention, integration, and differentiation.[12)14)15)] In addition, genetic modification of stem cells before application with the pro-survival gene Akt,[16)] vascular endothelial growth factor,[17)] or fibroblast growth factor 2[18)] promoted therapeutic efficacy.

Table 2 shows summarized results of MSCs therapy in porcine AMI model. The anatomy and physiology of the porcine heart is well known to be similar to a human heart, and it is considered that the porcine MI model is the best model for CVDs research. Cell number, delivery procedure, and surgical techniques in the porcine model are also similar to the clinical setting, and more realistic implications could be provided compared with a small animal model.

Running With Clinical Study

In AMI, cardiac muscle is damaged to become dysfunctional. After successful percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery with optimal medications, cardiac function is restored only to a limited degree {3-4% improvement in left ventricular ejection fraction (LVEF)} which may result in cardiac remodeling in approximately 60% of the patients with myocardial infarction.[19)20)]

Many clinical studies have proceeded for proving their safety and efficacy to reach a final goal "new therapy". Regarding cell type, most clinical trials have used unfractionated BMCs as the delivery product, postulating that stem/progenitor cells are the biologically applicable therapeutic agents. The most widely applicable technique for stem cell delivery is intracoronary infusion from a clinical standpoint.

The first human clinical trial of stem cell trial was intracoronary infusion of autologous BM unfractionated mononuclear cells to AMI patient.[21)] Subsequent clinical studies of stem cells for AMI were then initiated.

A variety of studies have demonstrated significant improvement of ventricular performance after stem cell therapy in AMI, resulting in an increase in LVEF and decrease in infarct size. In most cases, stem cell transplantation was performed in a time frame of 12 hours to several days after MI. Although there is large variability of hemodynamic data after cell therapy, there is moderate improvement of cardiac performance by stem cell therapy that is more quantitatively effective than therapeutic interventions and pharmacotherapy.[22)] Thus, autologous stem cell therapy represents an innovative and effective procedure for regeneration of impaired hearts in the early phase after the infarct.

As seen in Table 3, most recent clinical trials utilized BM-derived mononuclear cells isolated from patients after PCI. BM has been considered the safest source for autologous transplantation of stem cells, usually mononuclear cells, in clinical trials. For now the most widely used clinically approved source for stem cell therapy is autologous stem cells from BM (www.clinicaltrials.gov).

In addition to BM-mononuclear cells, MSCs are now actively under investigation for cardiac repair. BM contains a population of hematopoietic stem cells and a rare population of plastic-adherent stromal cells (1 in 10000 nucleated cells in BM).[23)]

These plastic adherent cells are MSCs capable of forming single-cell colonies, expansion in culture, differentiation into osteoblasts, chondrocytes, and adipocytes.[24)25)] MSCs were shown to be differentiated into a myogenic phenotype.[13)] Animal studies demonstrated that human MSCs could be transdifferentiated into endoderm-derived cells[10)] in injected myocardium, and coculture of MSC with ventricular myocytes induced transdifferentiation into a cardiomyocyte phenotype *in vitro*.[26)] Large-animal preclinical studies of MSCs administration in post-MI heart demonstrated the ability of MSCs to engraft, differentiate, and produce substantial functional recovery.[12)16)27)28)]

The therapeutic effect of MSC on AMI has been reported in four clinical trials. Chen et al.[29)] infused autologous MSC by intracoronary route and demonstrated regional wall motion and global LVEF were improved after six months of cell therapy. At that time, Vulliet et al.[30)] reported that a microinfarction occurred after intracoronary infusion of MSCs in a dog MI model. A Prochymal trial[31)] was designed to evaluate the safety of intravenous application of allogeneic BM-derived MSCs to AMI patients. According to animal studies, a large proportion of infused cells were trapped in the lungs after administration, raising potential concerns regarding compromised pulmonary function.[32)] The results of the Prochymal trial did not show any evidence of a pulmonary safety risk after infusion of allogeneic human (h)BM-MSCs. Instead, those data revealed improved pulmonary function in the MSC-treated patients, compared with baseline status. The rate of arrhythmia event was 4-fold lower in the hMSCs group than in the placebo group (8.8% vs. 36.8%, p=0.025). In ischemic cardiomyopathy, transendocardial injection of autologous BM-derived progenitor cells including mononuclear cells or MSCs produced functional recovery in scarred myocardium and reversed remodeling of the LV chamber.[33)] Unfortunately, however, they did not determine superiority between mononuclear cells and MSCs. Without the placebo control group, data from only 4 patients in each group were analyzed. The transendocardial autologous cells

Table 3. Summary of recent stem cell therapy trials in myocardial infarction (and heart failure)

Trial	Cell	Time of delivery (days after MI)	Results	F/U (months)	Patients (age)
van Ramshorst et al.[52]	Autologous BM-MNC, 1×10^8 cells, intramyocardial injection	Chronic myocardial ischemia	Modest improvement of summed stress score, LVEF in BMC group at 3 month, increase of quality of life at 6 month	3, 6	Placebo 25 (62), cell 25 (64)
Meyer et al., BOOST trial[53]	Autologous BMC, 24.6×10^8, IC	5 days	EF decrease by 3.3±9.5% in control, 2.5±11.9% in BMC Not promote a sustained improvement of EF	61	Control 30 (59.2), BMC 30 (53.4)
Tendera et al., REGENT trial[54]	BM-MNC (1.78×10^8), CD34+ (1.9×10^6), IC	PCI after 12 hour MI onset	EF: 39 to 39 in control, 37 to 40 in MNC, 35 to 38 in CD34+ group	6	Control 40 (59), non selected MNC 80 (55), selected MNC 80 (58)
Beitnes et al., ASTAMI trial[55]	BMC, 7×10^7, IC	4-7 day	Safe in the long-term, small ↑ in exercise time, no other effects in BMC group, echo con 46.9 to 46.8 BMC 45.7 to 47.5 MRI con 53.5 to 55.2 BMC 54.8 to 54.9	36	Control 50 (56.7), BMC 50 (58.1)
Hare et al., Prochymal[31]	Allogeneic BM-MSC, 0.5, 1.6, 5×10^6 cells/kg, iv	1-10 day	EF ↑	12	Placebo 21 (55.1), hMSC 39 (59.0)
Assmus et al., REPAIE-AMI[56]	Auto BMC, $236\pm174\times10^6$, IC	3-7 day after reperfusion	Still safe	24	Placebo 103 (57), BMC 101 (55)
Grajek et al.[57]	BMC, $2.34\pm1.2\times10^9$, IC	4-6 day after PCI	EF, LVEDV, LVESV, spiroergometric stress test: no difference	6, 12	Control 14 (50.9), BMC 31 (49.9)
Arnold et al., TECAM study[58]	BM-MNC, $97.6\pm61.4\times10^6$, IC	STEMI, <9±3 day of reperfusion	No difference in minimum lumen diameter, stenosis, changes in the contralateral artery, plaque volume	9	Control 37 (59.8), TECAM 37 (58.6)
Strauer et al., STAR-heart study[59]	BMC, $6.6\pm3.3\times10^7$, IC	Chronic HF EF <35% (mean post MI interval: 8.5 year)	Haemodynamics, exercise capacity, oxygen uptake, LV contractility, long-term mortality ↑ in BMC group	3, 12, 60	Control 200 (60), stem cell 191 (59)
Seth et al., ABCD trial-long term FU[60]	BM-MNC, IC (with coronary sinus blockage)	Dilated cardiomyopathy EF <35%	EF 5.4% ↑ (20±7.4 to 25±12), ESV ↓ (144 mL to 116 mL), EDV: no change at 6 mo EF ↑ (22.5±8.3 to 28.4±11.8), ESV ↓ at 36 mo	36	Control 20 (45), stem cell 24 (49)
Traverse et al.[61]	Auto BMC 1×10^8, IC	STEMI	EF 49±9.5 to 55.2±9.8, placebo EF 48.6±8.5 to 57±13.4, LVEDP ↓	6	Placebo 10 (57.5), BMC 30 (52.5)
Williams et al.[33]	Transendocardial, intramyocardial injection of auto BM-MNC (1 or 2×10^8), or MSC (1 or 2×10^8)	Ischemic cardiomyopathy	EDV (208.7±20.4 to 167.4±7.32 mL), infarct size ↓, regional function ↑ at 3 mo, changes in chamber dimensions not diff at 6 mo	12	Stem cell 8 (57.2)
Santoso et al.[62]	G-CSF (10 mg/kg/day) 5 days then PBSC harvested, recombinant erythropoietin (SQ inj) +PBSC 15 - 25×10^6, IC	15 day after PCI with DES within 15 day after onset	No diff in LVEDV, LVESV at 3 mo, but ↑ at 1 year	12-30	18 (55.4)
Mansour et al., COMPARE-AMI[63]	CD133+HSC, 1×10^7, IC	3-7 day after PCI	Safe, EF 41.2±1 at base, 51.1±2.5 at 4 mo, 52.3±2 at 12 mo	12	Placebo 20, cell 20 (52.2)

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Table 3. Continued

Trial	Cell	Time of delivery (days after MI)	Results	F/U (months)	Patients (age)
Hirsch et al., HEBE trial[64]	BM 296±164×10^6 or peripheral MNC 287±137×10^6	IC 4-7 day after MI	No difference (control 42.4±18.7%, BM 38.6±24.7, PB 36.8±20.9)	4	Control 65 (55), BMC 69 (56), PBMC 66 (57)
Penn et al.[65]	Allo MultiStem to the adventitia of the infarct-related vessel, 2×10^7, 6×10^7, 1×10^8	2-5 day after AMI	EF: 20 M (4.1% ↑), 50 M (8.7% ↑), 100 M (no change) LV stroke volume: control (-4.3 mL), 20 M (-3.6 mL), 50 M (+14.6 mL), 100 M (+7.9 mL)	4	Control 6 (53), MultiStem 20 million n=6 (64), 60 million n=7 (54), 100 million n=6 (53)
Bolli et al., SCIPIO[66]	CSCs, IC, 1 million (n=15), 0.5 million (n=1)	EF <40%, CABG, ischemic cardiomyopathy	EF 35.9% to 39.2% (4 mo), to 42.5% (12 mo), infarct size 32.6 to 24.8 (4 mo), to 22.8 (12 mo)	12	Control 7 (57.3), treatment 16 (56.0)
Moreira et al.[67]	BM-MNC 1×10^8, anterograde intra-arterial coronary (IAC) or retrograde intravenous coronary (IVC)	24 hour <MI, infract size >10%	Comparison of cell retention: IAC (16.14%), IVC (4.62%) at 4 hour, IAC (10.29%), IVC (3.13%) at 24 hour	24 hour	Control 6 (57.2), IAC 14 (59.7), IVC 10 (53.6)
Solheim et al.[68]	BM-MNC 68×10^8, IC	6 day after the STEMI	No changes in prothrombotic markers	3	Control 50, cell 50 (57.4)
Roncalli et al., BONAMI trial[69]	Auto BMC, IC	9.3 day after STEMI	Myocardial viability 16% (control), 34% (BMC), active significant adverse role of smoking	3	Control 49 (55), BMC 52 (56)
Ahmadi et al.[70]	BM-CD133+BMC, 1.77×10^6± 1.14×10^6 CD133+cells, intramyocardial transplantation	Candidate of CABG after MI	Safe, no benefit	60	Control 5, BMC 13

BM: bone marrow, EDV: end-diastolic volume, EF: ejection fraction, IC: intracoronary infusion, MNC: mononuclear cells, MSC: mesenchymal stem cells, BMC: bone marrow cell, MI: myocardial infarction, PCI: percutaneous coronary intervention, STEMI: ST segment elevation myocardial infarction, HF: heart failure, DES: drug-eluting stent, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end diastolic volume, LVESV: left ventricular end systolic volume, ESV: end-systolic volume, AMI: acute myocardial infarction, CABG: coronary artery bypass graft, PB: peripheral blood, LV: left ventricle, G-CSF: granulocyte colony stimulating factor, PBSC: peripheral blood stem cell, LVEDP: left ventricular end diastolic pressure, CSC: cardiac stem cell

in an ischemic heart failure trial (TAC-HFT) and Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis (POSEIDON) trials[34] are in progress to intensify those limitations (www.clinicaltrials.gov). TAC-HFT is designed for comparing BM-MSCs versus mononuclear cells, and POSEIDON is comparing the effects of allogeneic versus autologous MSC therapy in ischemic cardiomyopathy patients.

The delivery of MultiStem, an allogeneic BM-derived stem cell produced by Athersys, Inc. (Cleveland, OH, USA), to AMI patients has proved to be safe and well tolerated.[35] They showed MultiStem delivered via transarterial adventitia using a microsyringe catheter was safe with improvement of cardiac function in a dose-dependent manner.

Although the exact mechanism of MSC effects is still unresolved, accumulating results of large animal studies and clinical studies have shown that MSC-based therapy for cardiac repair is safe and provides substantial improvement in cardiac structure and function.

Looking Back With Consideration

The therapeutic effect of stem cell therapy on heart disease has been shown by experimental studies using small animal models. Results have been reported as extraordinarily promising with experimental results such as cardiomyogenesis, neovascularization, and paracrine effect on injured myocardium. Now we are facing challenges for bringing stem cells to clinically applicable therapeutics. Intracoronary transfer of autologous BMCs after optimum reperfusion therapy does not dramatically augment recovery of global LV function in patients, but could favorably affect cardiac remodeling after MI. Mixed results have been reported in clinical trials of stem cell administered patients after AMI with minimal improvement of ejection fraction or only a transient clinical benefit.

The different outcomes were attributed to differences in cell preparations, timing and method of cell administration, choice of endpoints, and characteristics of patients. Some studies failed to deter-

mine persistent clinical benefits after stem cell application (Table 3).

Arrhythmias have been reported to be associated with intramyocardial rather than intracoronary injection of stem cells in the early clinical studies; intramyocardial injection could be responsible for arrhythmogenesis. In addition, local injection induces a highly uneven distribution of cells, at least early after injection, which increases electrophysiological heterogeneity. Although recent available results of clinical experience[35)36)] so far suggest that proarrhythmic effects may be transient, cardiac arrhythmia occurs unpredictably, and long-term follow-up studies would be essential to understand the arrhythmogenesis induced by stem cell transplantation.

The most effective and safe cell type for myocardial repair and the clinical significance of cell therapy-induced arrhythmias will be determined in future pre-clinical and clinical studies.

There was a case report about fatal events after autologous hematopoietic stem cell application in a lupus nephritis patient.[37)] After direct renal injection of stem cells isolated from peripheral blood, masses at the sites of injection were developed with hematuria. Pathologic analysis revealed the masses were angiomyeloproliferative lesions and suggested to be a possible complication of stem cell therapy. There was no way to find out the detailed cause of death in those cases, but stem cell transplantation could be a causative event.

The ultimate goal of cell therapy is the regeneration of lost cardiac muscle along with the reversal of adverse remodeling. Despite growing clinical experience, the absence of standardized clinical end point in human trials has left us with fundamental questions. Issues to be addressed in the future include determining the ideal cell type, the cell number to be delivered, optimal cell isolation method, efficient cell storage, and optimal time of administration to improve the efficacy of the therapy. After that, more realistic and optimized conditions of stem cell therapy will be applied to patients suffered from CVDs with guaranteed safety.

The risk of exposing patients to possible adverse outcomes of cell therapy must be seriously considered before clinical application. The argument that clinical trials should be delayed till mechanisms are perfectly understood will deprive a large number of patients from therapeutic chances that may bring them clinical recovery. Stem cell therapy is a novel and innovative approach to cardiac therapeutics which has been achieved by numerous preclinical and early clinical studies showing safety, feasibility, and early efficacy.

Conclusion

Recent evidence from studies in animals and humans demonstrates the important roles of stem cells in CVDs. In this review, reports of recent clinical trials of stem cell therapy for myocardial infarction are summarized and some important considerations are suggested for further application. For now, the challenge is to improveme the scientific concept to clinical setting with current treatment modalities.

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