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REVIEW

Mesenchymal Stem/Stromal Cell-Based Therapy for Heart Failure
— What Is the Best Source? —

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Transplantation of stem/progenitor cells is a promising, emerging treatment for heart failure (HF) in the modern era. Mesenchymal stem/stromal cells (MSCs) are considered as one of the most promising cell sources for this purpose, because of their powerful secretion of reparative factors and immunomodulatory ability. To date, various sources of MSCs have been examined for the treatment of HF in preclinical or clinical studies, including adult tissues (bone marrow and adipose tissue), perinatal tissues (umbilical cord and amnion), and pluripotent stem cells (induced pluripotent stem cells and embryonic stem cells). Adult tissue-derived MSCs have been more extensively examined. Previous clinical trials have suggested the safety and feasibility of these MSCs in HF treatment, but their therapeutic effects remain arguable. Perinatal tissue-derived MSCs have the advantages of removing the necessity of invasiveness biopsy and of mass production. An increasing number of clinical studies (albeit early stage) have been conducted. Pluripotent stem cell-derived MSCs may be another promising source because of their mass-production ability underpinned by their unlimited expansion with consistent quality. However, the risk of tumorigenicity restricts their clinical application. In this review, we summarize the current information available from preclinical and clinical studies, highlighting the advantages and disadvantages of each MSC type. This will provide an insight into consideration of the best MSC source for the treatment of HF.

Key Words: Heart failure; Mesenchymal stem cells; Stem cell therapy

Heart failure (HF) is a leading cause of death and disability in many countries. The number of the affected is predicted to soar, along with the increase in the aged population.[1] This incurs a significant economic burden on society. The only established radical treatment for end-stage HF is cardiac transplantation; however, the availability of this treatment is limited by insufficient numbers of donors.[2] In addition, heart transplantation is highly expensive and associated with immunosuppression-related complications. Destination therapy using a left ventricular assist devise has potential to be an alternative, but requires further improvement, including attenuation of complications (i.e., anticoagulant-related and machine-related problems) before becoming an established therapy.[3] The current common treatment for HF is pharmacological, but the drugs developed so far have limited clinical efficacy particularly for severe HF. Therefore, development of effective alternative therapies for HF is highly desired.

Cell transplantation therapy has been considered as a promising treatment for HF. In the past 2 decades, many types of cells, including both pluripotent stem cells and adult tissue-resident stem/progenitor cells, have been proposed and examined in experimental and clinical research.[4] Pluripotent stem cells, including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), have an established capability to differentiate to cardiomyocytes (cardiac "regeneration"), but on the other hand such pluripotency can become a cause of teratoma formation.[4] In addition, inappropriate maturation and integration of cardiomyocytes derived from these cells may induce arrhythmias after transplantation.[5] In contrast, the clinical safety of adult tissue-resident stem/progenitor cells has been extensively reported. Although these cells rarely differentiate to cardiomyocytes after transplantation to the heart in vivo, they offer repair of the damaged myocardium (myocardial "repair") by their secretome (paracrine effect).[6] Mesenchymal stem/stromal cells (MSCs) are currently one of the most promising donor cell types, among the many types of adult stem/progenitor cells, including endothelial progenitor cells, skeletal myoblasts, cardiac resident stem/progenitor cells, and bone marrow mononuclear cells.[4] In fact, an increasing number of clinical trials using MSCs have currently been conducted or are planned.[7]

The terminology (i.e., mesenchymal stem or stromal cells) to describe MSCs used for cell therapy involves argument. As to the definition of mesenchymal "stem" cells, the International Society for Cell Therapy introduced 3 major criteria: (1) adherence to plastic under standard culture conditions, (2) expression of CD105, CD73 and CD90 but not CD45, CD34, CD14 or CD11b, CD79α or CD19, or HLA-DR surface markers, and (3) retain in vitro multilineage differentiation capacity into osteoblasts, chondroblasts,

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and adipocytes.[8] Only some of the previously used MSCs appear to meet these criteria. In addition, MSCs transplanted to the heart do not work or act as "stem cells" that differentiate to mesenchymal or other lineages. As such, we believe that most of the MSCs used for cell-based therapy for HF are better described as "mesenchymal stromal cells". As clear dissection between mesenchymal stem or stromal cells is difficult, this review includes all reports using cells considered to be mesenchymal stromal cells or mesenchymal stem cells.

A large number of preclinical reports have demonstrated the ability of MSCs to improve cardiac function in various types of experimental HF models.[9–11] Although cardiomyogenic differentiation of MSCs appears to be insignificant in vivo, MSCs are able to secrete a range of reparative molecules, including cytokines, chemokines, growth factors, microRNAs, and exosomes.[7] These beneficial secretomes result in anti-inflammation, neovascular formation, antifibrosis, and anti-apoptosis, leading to repair of damaged myocardium (paracrine effect). In addition, it has been suggested that MSCs can be used as allogeneic donors.[12] This will enable an off-the-shelf supply of quality-assured MSCs with reduced cost, thus allowing MSC-based therapy to be established as a widely-used standard treatment. However, the therapeutic effect of MSCs on cardiac function remains controversial in clinical studies and trials. Further optimization of the protocols is therefore needed for the future success of MSC transplantation therapy, and the decision of the most appropriate source for MSCs is a fundamental issue.

MSCs were initially identified in adult bone marrow, and subsequently found throughout the human body, including adipose tissue, muscles, tendons, dental pulp, skin, lungs, placenta, umbilical cord (UC), and amniotic fluid.[13] In addition, it has been reported that MSCs can be produced using pluripotent stem cells, including ESCs and iPSCs.[14,15] Among them, as the donor for HF, bone marrow-derived MSCs (BM-MSCs) were first used in animal as well as clinical studies, and have been the most extensively evaluated so far. Following this, adipose tissue-derived MSCs (AT-MSCs) and UC-derived MSCs (UC-MSCs) have been examined in preclinical studies and clinical trials. More recently, amnion-derived MSCs (AM-MSCs) and ESC/iPSC-derived MSCs have been proposed as promising cells for HF treatment. It is an important issue to decide which source is the most feasible and effective; however, a clear answer has not been obtained because the majority of previous studies were conducted independently using a wide range of protocols.

Key factors for MSCs to be ideal as the donor for cell therapy for HF include: (1) safety when injected in vivo, (2) absence of ethical issues, (3) able to induce myocardial repair and/or regeneration, (4) able to treat a wide range of HF types, including ischemic and nonischemic disease, (5) availability of mass production of high-quality, homogeneous cells, and (6) utility of allogeneic cells without immunosuppressive reagents. Factors 1–4 are no doubt crucial. The MSC-mediated therapeutic effect can be achieved through secretion of reparative factors (paracrine effect for myocardial repair), but cardiomyogenic differentiation (myocardial regeneration) may also have a role. Factors 5 and 6 are critical for MSC-based therapy to become a widely adopted treatment in the clinical arena. Autologous MSCs have disadvantages for factor 5, especially when the patients are elderly and have chronic HF and comorbidities including diabetes mellites.[16] This review aims to summarize the currently available preclinical and clinical information about the 5 major types of MSCs, with a particular focus on these key factors, and to discuss their advantages and disadvantages as a donor for cell therapy for HF.

Bone Marrow-Derived MSCs (BM-MSCs)

BM-MSCs are the most extensively investigated MSC type as the donor for MSC transplantation therapy for HF. In the 1970s, Friedenstein et al first reported a rare population of plastic-adherent, fibroblast-like, and colony-forming BMCs with a high replicative capacity, which are now commonly referred to as MSCs.[17] The basic protocol for collecting BM-MSCs from the product of bone marrow aspiration includes the following 3-step process: (1) separation of nucleated cells from nonnucleated cells by density gradient centrifugation, (2) adherence of cells to plastic tissue culture flasks, and (3) passaging of adhered MSCs.[18]

BM-MSCs are reported to have the capacity for cardiomyogenic differentiation in vitro,[19] in which bone morphogenetic protein (BMP)-2, fibroblast growth factor (FGF)-2, hepatocyte growth factor (HGF), insulin-like growth factor (IGF)-1, and transforming growth factor (TGF)-β1 play a role.[20–22] However, it is now agreed that BM-MSCs rarely differentiate to cardiomyocytes when transplanted into the heart in vivo.[7,23] Instead, tissue repair mediated by BM-MSCs' secretion is believed to be the major mechanism of the therapeutic effect for HF.[9] BM-MSCs secrete growth factors, cytokines, chemokines, microRNAs, and/or exosomes, which are potent for attenuating inflammation, improving neovascular formation, attenuating adverse remodeling, and/or inducing endogenous cardiac regeneration ("paracrine effects"). In addition, the secretome from BM-MSCs has immunosuppressive properties through modulation of T-cells, B-cells and monocytes.[24–26] Although this immunomodulating ability remains disputable,[27] this feature is important for a donor for cell therapy as it enables the use of allogeneic cells without immunosuppressive reagents.

There are a large number of preclinical in vivo studies that have examined the ability of BM-MSC transplantation to treat heart diseases. We summarize the key results as follows. Firstly, BM-MSC transplantation improves cardiac function in animal models of various types of heart disease, including acute/subacute myocardial infarction (AMI), ischemic cardiomyopathy (ICM), dilated cardiomyopathy (DCM), and myocarditis.[9–11] Secondly, MSC-based therapy using syngeneic, allogeneic or xenogeneic BM-MSCs is safe and has efficacy equivalent to that of autologous/syngeneic cells.[9] Thirdly, although the mechanism by which BM-MSCs improve cardiac function has not been fully confirmed, the paracrine effect, not cardiomyogenic differentiation, is likely to play a central role.[6] Finally, donor cell engraftment after BM-MSC transplantation using the current methods (i.e., intramyocardial (IM), intracoronary (IC), or intravenous (IV) injection) is not satisfactory,[28] which has encouraged development of a new, more effective cell-delivery methods (e.g., epicardial placement using bioengineering technology).[28–30]

Encouraged by these promising preclinical results, more than 20 clinical trials using BM-MSCs have been conducted for the treatment of HF (**Table 1**). The results collectively showed that transplantation of BM-MSCs was feasible and mostly safe. However, it is noteworthy that Gao et al reported a serious complication of coronary embolism during

Table 1. Clinical Trials of BM-MSC Transplantation for Heart Diseases

Reference	Study design	Disease	MSC type	Delivery route	Cell number ($\times 10^6$)	Concurrent procedure	Follow-up period (months)	Arms, case no.	Improvement in LVEF (vs. control)	Improvement in exercise tolerance (vs. control)
Chen et al[33]	Phase 2	AMI	Auto	IC	48,000–60,000	PCI	6	MSC 34, Control 35	Yes	Not shown
Hare et al[39]	Phase 1	AMI	Allo	IV	0.5, 1.6 or 5 /kg	PCI	6	MSC 39, Control 21	No	No
Yang et al[50]	Phase 1	AMI	Auto	IC	12.2, 13.2	PCI	6	Culprit coronary 8, Nonculprit coronary 8	No control	No control
Gao et al[31]	Phase 2	AMI	Auto	IC	3.08	PCI	24	MSC 21, Control 22	No	Not shown
Rodrigo et al[51]	Phase 1	AMI	Auto	IM	31	PCI	60	MSC 9, Control 45	No	Not shown
Lee et al[36] (SEED-MSC)	Phase 2/3	AMI	Auto	IC	72	PCI	6	MSC 33, Control 36	Yes	Not shown
Wang et al[52]		AMI	Auto	IC	200	PCI	6	MSC 28, Control 30	No	Not shown
Chullikana et al[40]	Phase 1/2	AMI	Allo	IV	2 /kg	PCI	24	MSC 10, Control 10	No	Not shown
Chen et al[53]	Phase 1/2	ICM	Auto	IC	5	PCI	12	MSC 24, Control 24	No	Yes
Mohyeddin-Bonab et al[54]		ICM	Auto	IM or IC	5.55	CABG or PCI	18	MSC 8, Control 8	No	Not shown
Hare et al[41] (POSEIDON)	Phase 1/2	ICM	Auto	IM	20, 100 or 200	None	13	20×10^6 MSCs 5, 100×10^6 MSCs 5, 200×10^6 MSCs 6	No control	No control
			Allo	IM	20, 100 or 200	None	13	20×10^6 MSCs 5, 100×10^6 MSCs 5, 200×10^6 MSCs 5	No control	No control
Mathiasen et al[55]	Phase 1/2	ICM	Auto	IM	21.5	None	36	MSC 31	No control	No control
Bartunek et al[34] (C-CURE)	Phase 2/3	ICM	Auto	IM	733	None	24	MSC 32, Control 15	Yes	Yes
Heldman et al[56] (TAC-HFT)	Phase 1/2	ICM	Auto	IM	200	None	12	MSC 22, Control 11	No	No
Karantalis et al[57] (PROMETHEUS)	Phase 1/2	ICM	Auto	IM	20 or 200	CABG	18	MSC 6	No control	No control
Mathiasen et al[37] (MSC-HF)	Phase 1/2	ICM	Auto	IM	77.5	None	12	MSC 40, Control 20	Yes	No
Guijarro et al[58] (MESAMI 1)	Phase 1	ICM	Auto	IM	61.5	None	24	MSC 10	No control	No control
Bartunek et al[38] (CHART-1)	Phase 3	ICM	Auto	IM	600	None	39 weeks	MSC 120, Control 151	No	No
Florea et al[42] (TRIDENT)	Phase 2	ICM	Allo	IM	20 or 100	None	12	20×10^6 MSCs 15, 100×10^6 MSCs 15	No control	No control
Perin et al[43]	Phase 2	ICM or NICM	Allo	IM	25, 75 or 150	None	36	MSC 45, Control 15	No	No
Ascheim et al[44]	Phase 2	ICM or NICM	Allo	IM	25	LVAD	12	MSC 20, Control 10	No	No
Butler et al[45]	Phase 2	NICM	Allo	IV	1.5 /kg	None	13	MSC 11, Control 12	No	Yes
Xiao et al[35]		DCM	Auto	IC	490	None	12	MSC 17, Control 20	Yes	No
Hare et al[46] (POSEIDON-DCM)	Phase 1/2	DCM	Auto	IM	100	None	12	Auto MSC 18	No control	No control
			Allo	IM	100	None	12	Allo MSC 19	No control	No control

Allo, allogeneic; AMI, acute myocardial infarction; Auto, autologous; BM-MSCs, bone marrow-derived mesenchymal stem/stromal cells; CABG, coronary artery bypass grafting; DCM, dilated cardiomyopathy; IC, intracoronary injection; ICM, ischemic cardiomyopathy; IM, intramyocardial injection; IV, intravenous injection; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MSC, mesenchymal stem/stromal cell; NICM, nonischemic cardiomyopathy; PCI, percutaneous coronary intervention.

IC injection,[31] which is a predicted risk from animal models.[32]

With regard to therapeutic efficacy, the majority of clinical studies have reported some clinical benefits of BM-MSC treatment, including reduced area of infarction, increased myocardial perfusion, decreased angina frequency, reduced hospitalization period, and clinical status. These favorable effects were observed not only in AMI and ICM patients, but also in nonischemic DCM patients. However, the number of trials revealing distinct improvement in more direct, objective and quantitative indicators (i.e., cardiac function or exercise tolerance) is not large. As a matter of fact, only 5 clinical trials have demonstrated improved left ventricular ejection fraction (LVEF) compared with an appropriate control group among 17 controlled trials listed in **Table 1**. Among the positive reports, 3 compared the absolute value of LVEF post-treatment[33–35] and the other 2 compared the change in LVEF between before and after treatment.[36,37] For example, the C-CURE trial, a prospective, multicenter, randomized trial of IM injection of autologous BM-MSCs pretreated with cardiogenic factors to patients with ICM, demonstrated improved LVEF in the BM-MSC treatment group, compared with control group, at 6 months.[34] Having said this, it is a fact that a larger number of clinical trials failed to show improvement of LVEF or exercise tolerance by BM-MSC transplantation therapy. Furthermore, it must be noted that the CHART-1 trial, the largest-scale phase III trial enrolling 271 patients, demonstrated no improvement in LVEF or exercise tolerance compared with control group at 39 weeks after IM injection of autologous BM-MSCs.[38] Although it is uncertain whether LVEF or exercise tolerance is the most reliable indicator when evaluating the therapeutic effect of stem cell therapy,[9] the results obtained so far collectively suggest that the therapeutic effects of current protocols of BM-MSC transplantation are not as substantial as predicted by preclinical studies.

It has been elucidated that the capabilities of transplanted BM-MSCs to survive, proliferate, and secrete deteriorate with aging and comorbidities such as diabetes of the donor,[16] limiting the application of autologous MSCs. Also, to establish an off-the-shelf use of MSCs, the use of allogeneic MSCs is essential. In this context, some clinical trials were performed to evaluate the safety and efficacy of allogeneic BM-MSCs.[39–46] The POSEIDON trial[41] and the POSEIDON-DCM trial,[46] which compared the safety and efficiency of transendocardial IM injection of autologous and allogeneic BM-MSCs, reported an absence of severe immunological response after allogeneic BM-MSC injection and similar therapeutic benefits between allogeneic and autologous BM-MSCs. Other trials agreed on improved clinical status of patients treated with allogeneic BM-MSCs. However, none of the trials reported significantly improved LVEF after allogeneic BM-MSC administration compared with appropriate control.

Cell dosage is another factor affecting therapeutic effects of MSC transplantation therapy. Perin et al compared the effects of 3 doses (25, 75 or 150×10^6 cells) of allogeneic BM-MSCs and showed beneficial dose-response effects for reducing major cardiac adverse events and attenuating LV remodeling.[43] Also, the TRIDENT trial, comparing 2 doses (20 or 100×10^6 cells) groups demonstrated improved LVEF and preserved serum pro-brain natriuretic peptide levels in the high-dose group.[42] Notably, the aforementioned 5 trials showing significantly improved LVEF after BM-MSC transplantation used relatively high numbers of cells ($>70\times10^6$).

It is true that BM-MSCs have been the most extensively used for clinical studies, but this cell type has several limitations compared with the other MSC types. Firstly, bone marrow aspiration is an established procedure but can be unexpectedly invasive for patients with severe HF, who also frequently have associated comorbidities.[13] On the other hand, collection of allogeneic BM-MSCs by invasive biopsy from healthy volunteers is associated with ethical issues. Secondly, as the initial yield of BM-MSCs from bone marrow aspirate is quite low (estimated at ≈0.001–0.01% of BM aspirate),[47] these cells need to be expanded with many passages to produce a sufficient number of cells for treatment.[47] Such a prolonged expansion procedure can, if excessive, reduce the functionality and quality of the cells.[48] It is also reported that higher passage MSCs are more likely to trigger an innate immune attack with allogeneic transplantation.[49]

Considering all this information together, BM-MSCs are still an important donor for cell transplantation therapy for HF. However, certain refinements of the treatment protocols to augment therapeutic efficacy will be needed for BM-MSCs to be clinically successful in the future. These may include the use of an optimal cell-delivery method and improvement of the cell culture protocol to expand BM-MSCs without losing cellular function.

Adipose Tissue-Derived MSCs (AT-MSCs)

In the 2000 s, a population of cells having MSC-like properties were discovered in human adipose tissue[59] and referred to as adipose-derived stem cells (ADSCs).[60] Technically, these cells do not always meet the conventional criteria of MSC[8] because they often express CD34 in their early passage.[61] However, immunophenotypes are >90% identical between ADSCs and BM-MSCs.[59] In this review, we use the term 'adipose tissue-derived MSCs (AT-MSCs)', which is conveniently used to describe all MSC populations harvested from adipose tissue, including ADSCs and others (e.g., adipose-derived regenerative cells (ADRCs), which are cells freshly collected from the stromal vascular fraction of the adipose tissue, comprised of leukocytes, smooth muscles, endothelial cells, and MSCs).[62]

AT-MSCs are isolated from the stromal vascular fraction of the white adipose tissue. With regard to donor cell production, AT-MSCs have a lot of possible advantages compared with BM-MSCs: Firstly, a more abundant tissue is accessible from throughout human body.[63] Secondly, the initial yield of AT-MSCs is greater (500-fold) and collected cells have a larger expansion potential than BM-MSCs.[64] Thirdly, AT-MSCs are less subject to cell senescence caused by repeated cell passage compared with BM-MSCs.[64,65] Fourthly, the cell isolation process is relatively simple, requiring only enzymatic digestion and/or mechanical separation, and does not require specific equipment.[63] Fifthly, AT-MSCs may have a superior ability to induce myocardial repair. Similar to BM-MSCs, AT-MSCs have a cardiomyogenic differentiation potential, at least in vitro, while their major mechanism for myocardial repair in vivo is highly likely to be a paracrine effect.[66] AT-MSCs are known to exhibit more angiogenic potential than BM-MSCs.[67] Finally, the immunomodulatory ability of AT-MSCs may be superior to that of BM-MSCs,[68] although this remains controversial.[69]

Preclinical in vivo therapeutic efficacy of AT-MSCs has been reported in many studies using a range of models of AMI[70,71] and ICM in rodents and swine.[72,73] Several comparison studies have claimed that AT-MSCs could achieve

Table 2. Clinical Trials of AT-MSC Transplantation for Heart Diseases

Reference	Study design	Disease	MSC type	Delivery route	Cell number ($\times 10^6$)	Concurrent procedure	Follow-up period (months)	Arms, case no.	Improvement in LVEF (vs. control)	Improvement in exercise tolerance (vs. control)
Houtgraaf et al[62] (APOLLO)	Phase 1/2	AMI	Auto	IC	20	PCI	6	MSC 10, Control 4	No	Not shown
Perin et al[74] (PRECISE)	Phase 1	ICM	Auto	IM	0.4, 0.8, 1.2 /kg	None	36	MSC 21, Control 6	No	Yes
Henry et al[75] (ATHENA I/II)	Phase 2	ICM	Auto	IM	40 or 80	None	12	MSC 17, Control 14	No	No
Qayyum et al[76] (MyStromalCell)	Phase 2	ICM	Auto	IM	72	None	6	MSC 41, Control 20	Not shown	No
Kastrup et al[77]	Phase 1	ICM	Allo	IM	100	None	6	MSC 10	No control	No control

AT-MSCs, adipose tissue-derived mesenchymal stem/stromal cells. Other abbreviations as in Table 1.

the same or even a higher degree of cardiac function improvement than BM-MSCs.[71,72] Cardiac function improvement after AT-MSC transplantation was associated with histological myocardial repair, including neovascular formation,[70,73] reduction in fibrosis,[70,71] and prevention of adverse ventricular remodeling post-MI.[73]

These favorable results of preclinical in vivo studies were followed by clinical studies for the treatment of HF, though the number of trials is much less than those using BM-MSCs (**Table 2**). The APOLLO Trial[62] has shown the safety and feasibility of IC injection of autologous ADRCs in conjunction with PCI, to treat AMI patients. Cardiac MRI and MIBI-SPECT showed a significant reduction of the infarct size post-AT-ADRC transplantation, but the increase in LVEF was not significant compared with controls. The PRECISE trial,[74] which injected ADRCs into ICM patients via the IM route, also showed no differences in adverse events between groups, but LVEF was not significantly improved by ADRC transplantation. However, at least, reduction in inducible ischemia and preservation of exercise tolerance were observed in the ADRC-treated patients compared with control group. The subsequent ATHENA I/II trial[75] demonstrated a reduction in HF hospitalizations and improvement in angina symptoms; however, again transplantation of AT-MSCs did not improve LV function or reduce cardiac dilatation. The MyStromalCell Trial[76] reported the feasibility and safety of IM injection of autologous vascular endothelial growth factor (VEGF)-A165-stimulated AT-MSCs for the treatment of patients with refractory angina. Unfortunately, their result failed to indicate increased exercise capacity by this treatment. More recently, allogeneic AT-MSCs were also tested. Kastrup et al[77] reported the safety and feasibility of IM injections of cryopreserved allogeneic Cardiology Stem Cell Centre adipose-derived stromal cell (CSCC_ASC) in patients with ICM. Although some patients developed donor-specific de novo HLA class I antibodies, there were no clinical symptoms or changes in inflammatory parameters. Thus, this treatment was suggested to be safe, but there was no significant improvement in LVEF from the baseline.

Taking all the reported clinical trial results together, transplantation of autologous AT-MSCs is feasible and safe in the clinical setting of HF. Allogeneic AT-MSCs appears to be safe but further long-term safety has to be studied in a larger number of cases. Improvement in global cardiac function was not significant in any of the previous clinical trials, and only 1 trial demonstrated improved excise tolerance and clinical performance. In addition, there are some considerations regarding AT-MSCs. Although surgical harvesting of adipose tissue is considered to be minimally invasive, there is a risk of venous/pulmonary embolism, injury of other organs and sepsis.[78] This complication may be infrequent but can be fatal. Similar to BM-MSCs, reduced quality of cells with senescence, aging, and comorbidities such as diabetes are a concern for the use of AT-MSCs. Future preclinical studies as well as clinical studies (i.e., appropriate large-scale phase III studies) are warranted for AT-MSCs to be established as a clinical treatment for HF.

UC-Derived MSCs (UC-MSCs)

UC is a perinatal tissue containing 2 umbilical arteries and 1 umbilical vein, both being embedded within a specific mucous connective tissue known as Wharton's jelly, which is covered by amniotic epithelium.[79] MSCs can be isolated from the UC by enzymatic digestion methods.[79] As UC can be obtained as medical waste after delivery, it is an attainable MSC source without the requirement of invasive biopsy or ethical concerns.

As perinatal tissue-origin cells, UC-MSCs present a more primitive phenotype and exhibit longer telomeres and active telomerase compared with adult tissue-derived MSCs such as BM-MSCs and AT-MSCs.[80] Therefore, UC-MSCs exhibit a greater proliferative ability, even after cryopreservation, and have less cellular senescence compared with adult counterparts.[81] In addition, UC is a quite large tissue, having an average size of 1.6 cm in diameter×30 cm in length. One UC offers a yield of approximately 1×10^7 MSCs before the first passage.[82] This will be able to produce $>1\times10^{10}$ MSCs within 1 month because of their vigorous proliferation.[82]

Because of the nature of the source tissue, UC-MSCs are usually used as allogeneic donors. This is likely to be feasible because UC-MSCs exhibit relatively low immunogenicity as a result of their limited expression of MHC I and lack of MHC II molecules and costimulatory antigens such as CD80 and CD86,[83] and they also have an immunosuppressive secretome.[81] These features are reported to be equivalent to or greater than those of adult tissue-derived MSCs. Indeed, preclinical studies demonstrated transplantation of human UC-MSCs resulted in myocardial repair in rodent,[84] rabbit,[85] and swine[86] models, despite being xenotransplantation without immunosuppressive reagents. In addition, it was reported that IV injection of allogeneic UC-MSCs

Table 3. Clinical Trials of UC-MSC Transplantation for Heart Diseases

Reference	Study design	Disease	MSC type	Delivery route	Cell number ($\times 10^6$)	Concurrent procedure	Follow-up period (months)	Arms, case no.	Improvement in LVEF (vs. control)	Improvement in exercise tolerance (vs. control)
Musialek et al[91]		AMI	Allo	IC	30	PCI	12	MSC 10	No control	No control
Gao et al[92]	Phase 2	AMI	Allo	IC	6	PCI	18	MSC 58, Control 58	Yes	Not shown
Li et al[90]		ICM	Allo	IC	3, 4, 5	None	24	MSC 15	No control	No control
Fang et al[94]		ICM	Allo	IV	5–10	None	12	MSC 3	No control	No control
Can et al[95] (HUC-HEART) (Preliminary result)	Phase 1/2	ICM	Allo	IM	20 /kg	CABG	6	MSC 18, Control 4	Not shown	Not shown
Zhao et al[93]		ICM or NICM	Allo	IM	Not shown	None	6	MSC 30, Control 29	Yes	Yes
Bartolucci et al[81] (RIMECARD)	Phase 1/2	ICM or NICM	Allo	IV	1 /kg	None	12	MSC 15, Control 15	Yes	No

UC-MSCs, umbilical cord-derived mesenchymal stem/stromal cells. Other abbreviations as in Table 1.

achieved comparable improvement in cardiac function to that of allogeneic BM-MSCs in a rat AMI model.[87]

Similar to other types of MSCs, UC-MSCs appear to have the potential to differentiate into cardiomyocytes. 5-azacytidine induces expression of Notch1, DLL4, GATA4, and Nkx2.5 in UC-MSCs,[88] and encourages UC-MSCs to differentiate into cardiomyocyte-like cells by activating the extracellular regulated kinase pathway.[89] Having said this, the major mechanism for UC-MSC-derived myocardial recovery in vivo is again believed to be the paracrine effect.[86] Paracrine effects of UC-MSC include increased angiogenesis,[84–86] decreased apoptosis,[84,86] reduction in fibrosis,[83,86] immunosuppression,[85] and recruitment and differentiation of endogenous cardiac stem cells.[84] These are likely to collectively result in increased global cardiac function[83,85,86] and prevention of ventricular dilatation.[83,84] Of note, 1 study has demonstrated that UC-MSCs have a putative higher tissue-repair paracrine potential compared with adult tissue-derived MSCs.[81] UC-MSC-mediated myocardial repair has been observed not only in ischemic heart disease models such as AMI and ICM, but also in nonischemic DCM models.[83]

Based on these promising results from preclinical studies, clinical trials have been conducted since the early 2010s. To date, 7 clinical trials have tested human UC-MSCs for the treatment of AMI and chronic HF, including both ICM and nonischemic cardiomyopathy (**Table 3**).[81,90–95] A full range of IC, IM and IV injections were used as the cell-delivery route. These are phase I or II clinical trials and safety was the primary endpoint in almost all of the studies. As a result, safety of allogeneic UC-MSCs was suggested; no major adverse effects were observed. Although it may not be appropriate to discuss therapeutic efficacy based on these early-phase, small-scale clinical trials, 3 out of 4 controlled studies demonstrated that UC-MSC transplantation improved LVEF compared with control (the remaining study has not disclosed final results). In addition to the improvement in global LV function, Gao et al[92] reported the prevention of adverse cardiac remodeling in AMI patients who received an IC infusion of UC-MSCs. In addition, significant improvements were noted in exercise tolerance and clinical status after UC-MSC treatment. Zhao et al reported an increase in 6-min walking distance and a decrease in serum B-type natriuretic peptide levels in patients with severe systolic HF.[93] Bartolucci et al reported an improved NYHA class and quality of life (as assessed with Minnesota Living with Heart Failure Questionnaire) in chronic HF patients.[81]

To summarize, UC-MSCs are derived from perinatal tissues and available without invasive biopsy or ethical concerns. Preclinical studies suggest that UC-MSCs have a greater capability of proliferation, senescence-resistance and immunosuppression compared with adult tissue-derived MSCs. Early-phase clinical trials to date have demonstrated that transplantation of allogeneic UC-MSCs is safe and would be effective to treat HF patients, albeit preliminarily. Thus, UC-MSCs have great potential as a donor for cell therapy and further preclinical studies and further larger-scale, randomized, controlled, multicenter phase III clinical trials are warranted. Establishment of appropriate facilities to produce large-scale, good manufacturing practice (GMP)-compliant UC-MSCs is also essential for off-the-shelf clinical use of UC-MSCs.

Amnion-Derived MSCs (AM-MSCs)

More recently, another prenatal tissue, the amniotic membrane, has been a target of growing interest as an alternative source of MSCs. Amnion is the inner membrane of the fetal membrane that surrounds the embryo and can be peeled off the outer chorionic membrane by blunt dissection.[13] Human amniotic membrane is approximately 40×40 cm in size on average and contains a large quantity of MSCs, which originate from the fetal mesoderm. As many as approximately 1×10^7 AM-MSCs can be obtained from one amnion (unpublished data), and AM-MSCs have the characteristics of perinatal cells (i.e., greater proliferative ability and less cellular senescence vs. adult tissue-derived MSCs). Thus, mass production of less-passaged MSCs is possible with AM-MSCs.[96] AM-MSCs share similar properties with the other perinatal tissue-derived MSCs, UC-MSCs. However, there is also some diversity in the gene expression profile between these MSCs.[97–99]

Cardiomyogenic differentiation of AM-MSCs has been reported in vitro and in vivo.[100,101] Interestingly, undifferentiated AM-MSC express GATA4, Nkx2.5, myosin light chain (MLC)-2a, MLC-2v, cardiac troponin-I (cTnI), cardiac

troponin-T (cTnT), and the α-subunits of the cardiac-specific L-type calcium channel (α1c) and the transient outward potassium channel (Kv4.3).[100] The cardiomyogenic potency of AM-MSCs is reportedly improved by FGF-2, activin A, IL-10, or progesterone.[102,103] One report demonstrated that engrafted AM-MSCs expressed von Willebrand factor, α-smooth muscle actin (αSMA) or cTnI, suggesting differentiation to 3 major cardiac cell types: endothelial cells, smooth muscle cells and cardiomyocytes.[101] Having said this, a more convincing mechanism for AM-MSCs induction of therapeutic effects will be based on their secretome. Human AM-MSC secrete significant levels of angiogenic factors and cytoprotective cytokines, generally similar to other MSC types.[96] However, such paracrine factor secretion is reported to be distinct between AM-MSCs and UC-MSCs.[97–99] AM-MSCs exhibit significantly greater production of prostaglandin E2 (PGE2), VEGF and epidermal growth factor (EGF), whereas UC-MSCs showed higher production of TGF-β, matrix metalloproteinase (MMP)-8 and HGF.

It is most likely that AM-MSCs will be transplanted to allogeneic patients in the clinical scenario. Human AM-MSCs exhibit strong immunomodulatory effects by their secretion, including PGE2, which reduces T-cell proliferation.[96] In addition, similar to UC-MSCs, AM-MSCs express limited levels of HLA-A and -B and do not express HLA-DR, presenting a low immunogenic profile.[102] These features enabled successful xenogeneic transplantation of human AM-MSCs to wild-type rodents without using immunosuppressive reagents.[103] Transplantation of human AM-MSCs into NOD/SCID mice with AMI enabled engraftment of human AM-MSCs in rodent hearts and improved LV function in association with increased capillary density, angiogenic cytokine levels, angopoietin-1 and VEGF-A levels.[104] In another study using an ischemia-reperfusion model in swine, improved viability in the peri-infarct region, improved regional contractility and LVEF, and reduced cardiac dilatation were observed after transplantation of human AM-MSCs.[105]

One study compared the therapeutic efficacy between allogeneic rat fetal membrane-derived MSCs (FM-MSCs) and syngeneic BM-MSCs in a rat ICM model.[106] In some studies, using rodent models, FM-MSCs were used as a model of AM-MSCs, because of the technical difficulty in separating the amnion from the chorion. MSCs were transplanted onto the surface of the infarcted myocardium by the cell sheet method. FM-MSCs improved cardiac function, increased capillary density and reduced myocardial fibrosis to the same extent as BM-MSCs, compared with the untreated group. The engraftment rate of transplanted cells and immune cell infiltration into the transplanted area did not differ between the 2 types of MSC transplants. A small number of engrafted MSCs differentiated into vascular structures and were positive for lectin I and αSMA.

To date, no clinical application of AM-MSCs has been facilitated yet for the treatment of cardiovascular diseases, but a phase I/II trial for treating Crohn's disease is about to start in Japan.[107] MSCs derived from the placenta, including amnion, have been clinically examined in various diseases other than cardiovascular diseases, such as multiple sclerosis,[108] idiopathic pulmonary fibrosis,[109] and type 2 diabetes.[110] Thus far there are no reports showing any serious side effects, implying that AM-MSC transplantation may be safe.

To summarize, although clinical trials have not been initiated, the results of in vivo preclinical studies suggest that transplantation of AM-MSCs is a promising approach for the treatment of HF. In addition to the paracrine secretome-mediated myocardial repair, this MSC type may be able to generate new cardiomyocytes via differentiation. Their immunomodulatory effect is also strong; even xenotransplantation is successful, validating the use of allogeneic AM-MSCs. Furthermore, AM-MSC have an advantage in mass production of less-passaged MSCs, compared with adult tissue-derived MSCs. Further preclinical and clinical studies to confirm the safety and efficacy of AM-MSCs are justified.

Pluripotent Stem Cell-Derived MSCs

It is now possible to generate MSCs in vitro from other stem cells, including ESCs and iPSCs. Although tissue-derived MSCs have a limited source with a restricted proliferation capacity in vitro because of replicative senescence,[48] ESC/iPSC-derived MSCs are a theoretically unlimited source because of their self-renewal ability.[111,112] This makes this MSC type extremely attractive. Although ESCs are associated with ethical issues, these cells appear to be more stable, at least with current technologies, compared with iPSCs.[113]

ESC/iPSC-derived MSCs are reported to be in a transitional state of development (between stem cells and terminally differentiated cells).[114] However, these MSCs exhibit typical MSC morphologies and surface marker expressions, as well as multipotency to differentiate into adipogenic, chondrogenic, and osteogenic lineages.[111,112] Cardiomyogenic differentiation was also reported. Human ESC-MSCs presented more dynamic cardiomyogenic differentiation compared with tissue-derived MSCs when cocultured with neonatal rat cardiomyocytes.[23]

ESCs and iPSCs can be expanded in vitro without undergoing senescence, so these cells may provide an unlimited number of early passage MSCs for treatment. In addition, previous studies demonstrated that these MSCs are more proliferative, in association with longer telomeres,[115] compared with adult or fetal tissue-derived MSCs.[116,117] It was reported that the genes related to control of DNA replication and repair are highly upregulated in ESC-derived MSCs compared with BM-MSCs, which may partly explain the improved proliferation potential.[118]

ESC/iPSC-derived MSCs have low immunogenicity because they lack HLA-II, similar to traditional MSC lines. Besides, these MSCs are less sensitive to proinflammatory IFN-γ-induced HLA-II expression than adult and fetal tissue-derived MSCs, suggesting that ESC/iPSC-derived MSCs are less prone to immunological rejection after transplantation in vivo.[119] Also, ESC/iPSC-derived MSCs modulate the activity of T-cells,[116] natural killer (NK) cells,[120] and dendritic cells[121] more effectively than adult tissue-derived MSCs. Taken together, allogeneic ESC/iPSC-derived MSC might be able to establish an immune-privilege status in the heart.

As regards the paracrine effect, ESC/iPSC-derived MSCs exhibit a powerful secretion of cytokines and growth factors to induce myocardial repair. It was reported that iPSC-MSCs express higher levels of cardioreparative cytokines, such as stromal cell-derived factor (SDF)-1a, stem cell factor, and FGF-2, compared with BM-MSC.[112] Also, ESC/iPSC-derived MSC secrete an increased level of anti-inflammatory and reparative cytokines, including IL-10 and EGF, and lower levels of proinflammatory cytokines

such as IL-6 compared with tissue-derived MSCs.[117]

There is preclinical evidence supporting the safety and efficacy of ESC/iPSC-derived MSCs in vivo. Simpson et al demonstrated that transplantation of a collagen patch containing human ESC-MSCs onto the heart of athymic nude rats with AMI exerted equivalent therapeutic efficacy with regard to attenuating adverse LV remodeling and maintaining diastolic function as BM-MSCs.[122] Augmented neovascular formation was inferred as a key mechanism for these therapeutic effects of ESC-MSCs. Similarly, Miao et al showed that IM injection of iPSC-MSCs alleviated ventricular remodeling and preserved myocardial strain in mice with AMI, which was mainly attributed to paracrine effects.[15] Zhang et al[14] examined these paracrine effects by using conditioned medium harvested from iPSC-MSCs. After IM injection of the conditioned medium into mice with anthracycline-induced cardiomyopathy there was enhanced alleviation of LV dysfunction and dilatation, less cardiomyocyte apoptosis and fibrosis, compared with conditioned medium harvested from BM-MSCs.

In summary, research to date suggests that ESCs and iPSCs are highly promising sources of MSCs. ESC/iPSC-derived MSCs have the great advantage of being an unlimited source and generating large amounts of high-quality MSCs because of their high proliferative ability without senescence. However, it is apparent that ESC/iPSC-derived MSCs have to be further investigated in experimental models in vitro as well as in vivo. In particular, these MSCs may be contaminated with undifferentiated iPSC/sESCs, and are associated with a potential risk of tumor formation. This issue has to be fully addressed with extreme caution before these MSCs are transplanted into patients. In addition, long-term stabilization of the phenotype of ESC/iPSC-derived MSCs needs to be confirmed in vitro and in vivo.[121,123]

Conclusions

This review summarizes the preclinical and clinical information regarding the major types of MSCs used for the treatment of HF, comprising BM-MSCs, AT-MSCs, UC-MSCs, AM-MSCs, and ESC/iPSC-MSCs. These MSCs each have their own strengths and weaknesses as the ideal source for clinical MSC-based therapy. As regards availability for mass production and off-the-shelf supply, perinatal tissue-derived MSCs, including UC-MSCs and AM-MSCs, as well as ESC/iPSC-MSCs, appear to have an advantage. Research has suggested that all these MSCs types have the potential to be used as allogeneic donors; however, there are also controversial results, requiring further in vivo and in vitro studies to conclude this feature. BM-MSCs, AT-MSCs, and UC-MSCs have been transplanted into human patients, and the safety of these cells, both autologous and allogeneic, has been proven, but continuous care is needed in future clinical trials. ESC/iPSC-MSCs require more intensive safety investigations before clinical application because these cells have a higher risk of tumor formation (teratoma formation).

The therapeutic potential of all MSC types has been well described in preclinical studies, but therapeutic efficacy in clinical trials has not been satisfactory, particular for BM-MSCs and AT-MSCs. It is not appropriate to determine the most potent MSC type in terms of therapeutic potential from currently available information. To perform an appropriate comparison, the optimized conditions of each MSC type (the most effective cell number transplanted, the most efficient route for cell delivery, and the optimized cell preparation processing) need to be used for each of the different HF types, including AMI, ICM etc., in animals or more preferably patients. Although it is now widely believed that the major mechanism by which MSC transplantation improves cardiac function is the paracrine effect, the details of this mechanism, as well as involvement of cardiomyogenic differentiation, have to be further elucidated.

The best source for MSC transplantation therapy for HF should be decided based on further accumulated information on each MSC type. Continuous optimization of each MSC type, well-designed comparative studies between different MSC sources and detailed mechanistic studies at both the preclinical and clinical level are warranted to this end, and such results will also be critical for the future success of MSC transplantation therapy for HF.

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Conflict of Interest

None.

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