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Therapeutic efficacy of mesenchymal stem cells for cardiovascular diseases

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ABSTRACT

Despite the improvements in pharmacological and surgical treatments, cardiovascular diseases (CVDs) are the number one cause of death worldwide. During the last two decades, the search for new therapies has been revolutionized with the growing knowledge of stem cell biology. Due to their huge differentiation capacity and paracrine effects, mesenchymal stem cells (MSCs) are a promising tool for the treatment of CVDs. The encouraging outcomes of preclinical studies using MSCs as a treatment for diseased myocardium have set the scene for worldwide clinical trials. In this review, we overview either complete or ongoing clinical trials using MSCs for the therapy of CVDs. In particular, we analyze the biological properties of MSCs, elucidate recent clinical findings and clinical trial phases of investigation, highlight clinical therapeutic effects of MSCs, and discuss challenges towards the clinical use of these cells in the therapy of CVDs.

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Introduction

The leading cause of mortality and disability worldwide are cardiovascular diseases (CVDs), systemic circulatory diseases which arise in the field of abnormal heart and blood vessels. CVDs accounted for approximately 31% of all global deaths, causing 17.8 million deaths in 2017, mostly in low- and middle-income countries [1]. Hypertension, diabetes, hyperlipidemia, tobacco use, obesity, a sedentary lifestyle and the harmful use of alcohol are the pivotal risk factors for CVDs occurrence [2]. In spite of the notable progress in medical and surgical therapies, CVDs continue to exhibit high rates of morbidity and mortality. Drug therapy problems and cardiotoxicity are some of the biggest barriers to pharmacotherapy in the treatment of CVDs [3]. Fever, postoperative bleeding, stroke, atrial fibrillation, renal failure, respiratory distress, cardiogenic shock, and myocardial infarction type 5- represent the ordinary complications that can occur as a consequence of the surgical treatment in patients with CVDs [4,5]. Likewise, these therapeutic problems prolong hospital stays and increase the overall burden of healthcare expenditures. Therefore, a certainty has developed for therapy that it has fewer side effects, lower mortality rates, fewer complications, as well as better and secure recoveries of patients.

With the recent advances in the field of stem cell biology [6], it was suggested that stem cells might be exploited to repair damaged cardiac tissue and blood vessels. In this review, we overview either complete or ongoing clinical trials using MSCs for CVDs conducted worldwide. In particular, we analyze the biological properties of MSCs, elucidate recent clinical findings and clinical trial phases of investigation, highlight the clinical therapeutic effects of MSCs, and discuss the

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challenges towards the clinical use of these cells in the therapy of CVDs.

Discussions

Mesenchymal stem cells - a new therapeutic strategy for cardiovascular diseases

Mesenchymal stem cells are adult stem cells that can be isolated from nearly every tissue type in the adult or infant human body [7] such as bone marrow [8], adipose tissue [9], peripheral blood [10], synovium, and synovial fluid [11], menstrual blood and endometrium [12], skin [13], the dental pulp [14], umbilical cord blood [15], Wharton's jelly [16], amniotic fluid and placenta [17], breast milk [18], and urine [19] (Figure 1). Usually, MSCs are plastic-adherent, fibroblast-like cells that are qualified to differentiate to osteoblasts, chondroblasts, and adipocytes in vitro [20]. MSCs are able to transdifferentiate into non-mesodermal cells such as neurons or astrocytes, hepatocytes, and pancreatic cells under specified culture conditions [21]. Due to the absence of an MSC-specific marker, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposed a minimum number of criteria for the phenotypic characterization of human MSCs [22]. MSCs are positive for CD105, CD73, and CD90 and characterized by the lack of expression CD45, CD34, CD14, CD11b, CD79 alpha or CD19, and HLA-DR surface molecules [22].

A tremendous number of animal models that resemble the pathology of CVDs in humans have demonstrated not only the therapeutic efficacy of culture-expanded MSCs, but also their mechanism of action that may be of relevance to the future widespread clinical use of MSCs [23-30]. MSCs represent a cellular source for cardiovascular repair since they are able to differentiate into cardiomyocytes (CMs) [31-33], endothelial cells (ECs) [34-36], and smooth muscle cells (SMCs) [36-38] (Figure 1). However, very few MSCs are found engrafted at the site of injury linked to the degree of functional recovery [7,21]. Thus, the vast majority of recently published studies revealed that the beneficial effects and utilization of MSCs in CVDs will be also based on their ability to produce a wide range of cytokines, chemokines, and growth factors [39] that resolve inflammation [24], inhibit apoptosis [26,27] and fibrosis [26,40], promote angiogenesis [25,29,40-50], and induce endogenous cardiomyocyte regeneration [43-45] (Figure 1).

MSCs attenuate cardiac injury through the production of several pro-angiogenic factors such as the placental growth factor (PGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF-1), and basic fibroblast growth factor (bFGF), which facilitate tissue regeneration by inducing the proliferation of ECs and by promoting neovascularization [25,26,29,40-42,46]. In cell-to-cell contact and through the production of soluble mediators, MSCs can alter the function of all immune cells that have a key role in the pathogenesis of CVDs [47,48]. MSCs regulate the proliferation, activation, and effector function of T lymphocytes, professional antigen-presenting cells (dendritic cells, macrophages, B lymphocytes), NK cells, and NKT cells [48,49]. Thus, the improvement of a wide range of cardiac functions (increased EF, decreased in scar tissue, reversed remodeling, ameliorated contractility, augmented heart perfusion, and improved blood vessel density) [30,41,50-52], indicates the possible use of MSCs in the therapy of CVDs. Over the past few years, MSCs were used in a broad range of clinical trials exploring the therapeutic effects of MSCs in the treatment of coronary artery disease, heart failure, and cardiomyopathy (Table 1), as well as peripheral artery disease and stroke (Table 2) and their findings, were analyzed in this review.

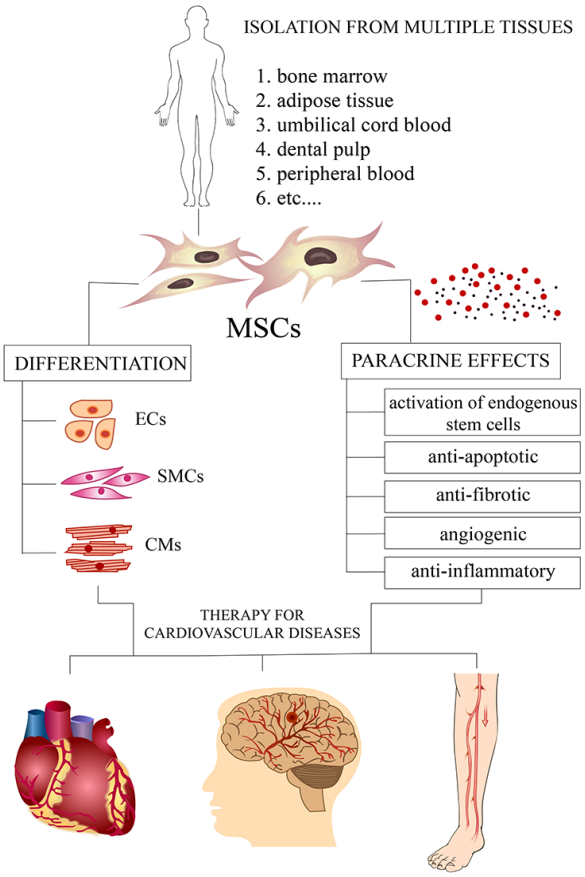

Figure 1. The main mechanisms responsible for MSC-based treatment of CVDs. Transplanted MSCs can contribute to cardiovascular repair and regeneration by forming endothelial cells (ECs), smooth muscle cells (SMCs) and cardiomyocytes (CMs) (differentiation). Additionally, MSCs produce a broad range of cytokines, chemokines, and growth factors that resolve inflammation, inhibit apoptosis and fibrosis, promote angiogenesis, and induce endogenous cardiomyocyte regeneration.

MSC-based therapy of coronary artery disease

One study showed that one month after ST-elevation MI (STEMI), the intracoronary infusion of autologous bone marrow-derived MSCs (BM-MSCs) provided a modest improvement in the left ventricular ejection fraction (LVEF) at six-months follow-up by single-photon emission computed tomography [51]. It is also important to notice that there was no treatment-related toxicity during the administration of MSCs, and no serious cardiovascular complications throughout the follow-up [51]. For the reason that cell therapy is not possible at an early phase of remodeling, growing evidence recommends that the prevention of LV remodeling by MSCs transplantation throughout the late dilation phase is practical [53]. As a proper technique for supplementing primary percutaneous coronary intervention (PCI), several research groups investigated intracoronary transplantation of autologous BM-MSCs [53,54].

In patients with acute anterior wall MI, they found that the administration of autologous BM-MSC at one month after PCI is tolerable and safe with a significant improvement in LVEF one month and four months after the stem cell treatment [54]. Serial cardiac echocardiographic monitoring displayed that the improvement of the cardiac function was kept nearly six months after the procedure [53]. At the 16–36- month follow-up, the implanted cardioverter defibrillators failed to discover sustained or non-sustained ventricular arrhythmia in any patient with previous anteroseptal MI who underwent intracoronary transplantation of autologous BM-MSCs [55]. MSCs may be used as an allogeneic graft for the treatment of CVDs, due to the lack of various major histocompatibility complex and costimulatory cell-surface antigens [56,57].

In a randomized, double-blind, placebo-controlled study, Hare and co. showed that the intravenous administration of allogeneic BM-MSCs (0.5, 1.6, and 5.0×10^6 MSCs/kg body weight) is well-tolerated, safe, and effective in patients after acute anterior MI [58]. In the same study, they showed that LVEF, forcible expiratory volume and global symptom score were significantly improved, while the incidence of arrhythmia was reduced in MSC-treated compared to placebo-treated post-infarction subjects [58]. In a double-blind, randomized controlled trial of Gao and co., it was elucidated that the intracoronary application of WJMSCs in patients with acute STEMI significantly increased myocardial viability, perfusion within the infarcted territory, as well as the global LVEF [52]. WJMSC infusion averted post-infarct LV adverse remodeling, as evidenced by the modifications in the LV end-systolic volumes (LVESV) and end-diastolic volumes (LVEDV) at 18 months [52] (Table 1).

MSCs as novel therapeutic agents in the treatment of heart failure

It was demonstrated that intra-myocardial injections of autologous BM-MSCs were safe and improved the myocardial function in patients with ischemic HF, compared to placebo in terms of LVEF, stroke volume, myocardial mass, and cardiac output [59,60]. The administration of BM-MSCs, as evidenced by progressive decreases in both LVEDV and LVESV, led to reverse LV remodeling, indicating an improved outcome in patients with HF [59,60].

In patients with ischemic or non-ischemic HF, Perin and co. evaluated the feasibility and safety of different doses (25, 75, or 150 million cells) of immune-selected allogeneic mesenchymal precursors cells (MPCs [61]. They found that the transendocardial route of delivery for MPCs therapy was safe and well-tolerated without clinically symptomatic immune responses [61]. The highest MPCs dose diminished the adverse cardiac events and reversed certain parameters of cardiac remodeling in HF patients [61]. Nevertheless, further studies are needed to explore the relationship between the number of intramyocardial injections, the number of stem cells and the volume administered, and their impact on the observed reverse remodeling outcome. Kastrup and co. formed a centralized production of an allogeneic Cardiology Stem Cell Centre adipose-derived stromal cell (CSCC_ASC) product from healthy donors that delivered directly to the myocardium into the border area of infarcted tissue and showed safety, feasibility, and a tendency toward clinical efficacy in ten patients with ischemic heart disease and ischemic HF [62]. It is important to notice that none of the patients had any clinical symptoms or changes in biochemical parameters or inflammatory signs implying immunization. With the aim of assessing changes in parameters such as LVEDV, LVEF, stroke volume, myocardial mass, cardiac output, and change in clinical symptoms in ischemic HF patients treated with CSCC_ASC, a double-blind, placebo-controlled, multicenter study is currently in phase II [63]. The umbilical cord-derived MSCs (UC-MSCs) are easily attainable stem cells and can differentiate into cardiomyocyte-like and ECs in vitro, and also exert paracrine effects that enhance vascular regeneration and cardiomyocyte protection. Due to concerns about the safety of donor cell entrapment in the pulmonary circulation and whether they will achieve their therapeutic effect in a context of low cardiac engraftment, there is limited experience on intravenous administration of MSCs in patients with CVDs [64]. The intravenous delivery of UC-MSCs seems safe and efficient in patients with chronic stable HF [64]. UC-MSC–treated group exhibited significant improvements in the ventricular systolic function, New York Heart Association functional classification (NYHA Classification), and quality of life indices [64] (Table 1).

Table 1. Clinical trials using MSCs to treat cardiac diseases

Disease	Source of MSCs	Administration route	Dose (cell number x 10^6)	Follow-up period (months)	Outcome (improvement in LVEF) (vs. control)	Ref.
AMI	auto-BM-MSCs	IC	48 000- 60 000	6	Yes	53
AMI	allo-BM-MSCs	IV	0.5, 1.6 or 5/kg	6	No	58
AMI	allo-WJMSCs	IC	6	18	Yes	52
AMI	auto-BM-MSCs	IC	72	6	Yes	51
AMI	auto-BM-MSCs	IC	72	4 and 12	Yes	54
IHF	auto-BM-MSCs	IM	53.8	6	Yes	59
HHF	auto-BM-MSCs	IM	600	13	Yes	60
IHD and IHF	allo-ASCs	IM	100	6	Yes	62
ICM or NICM	allo-BM-MPCs	IM	25, 75 or 150	36	No	61
HF	allo-AT-CSCC_ASC	IM	100	6	Yes	63
HF	allo-UC-MSCs	IV	1/kg	12	Yes	64
DCM	allo-BM-MSCs auto-BM-MSCs	IM IM	100 100	12 12	No control (yes) No control	57
ICM	auto-BM-MSCs	IM	200	12	No	66
ICM	auto-BM-MSCs	IM	20 or 200	18	No control	67
DCM	auto-BM-MSCs	IC	490	12	Yes	69
ICM	allo-BM-MSCs	IM	20 or 100	12	No control	70
ICM	auto-BM-MSCs allo-BM-MSCs	IM	20, 100 or 200	13	No control	68

Abbreviations: AMI- acute myocardial infarction; IHF- ischemic heart failure; ICM- ischemic cardiomyopathy; NICM- non-ischemic cardiomyopathy; DCM- dilated cardiomyopathy; IHD- ischemic heart disease; IHF- ischemic heart failure; auto- autologous; BM-MSCs- bone marrow-derived mesenchymal stem/stromal cells; allo- allogeneic; WJMSCs- Wharton's jelly-derived mesenchymal stem cells; ASCs- adipose derived stromal cells; MPCs- mesenchymal precursor cells, CSCC_ASC- Cardiology Stem Cell Centre adipose-derived stromal cell; AT- adipose tissue derived; UC-MSC- Umbilical cord–derived mesenchymal stem cells; IC- intracoronary injection; IV- intravenous injection; IM- intramyocardial injection.

MSCs as new agents in cell-based therapy of cardiomyopathy

Progressive disorders most often end with heart transplants and they are known as ischemic cardiomyopathy (ICM) and dilated cardiomyopathy (DCM). Given the fact that MSCs secrete numerous paracrine factors that attenuate these mechanisms and possess immunomodulatory properties, they are a promising therapy for both forms of cardiomyopathy [65].

For patients with chronic ICM and LV dysfunction, it was shown that transendocardial and intramyocardial injections of autologous MSCs were safe [66,67]. MSCs improved the cardiac structure and function through several mechanisms such as reducing fibrosis and

promoting neoangiogenesis and neomyogenesis [67]. Increased viable myocardial mass and decreased scar size suggested a true MSC-mediated myocardial regeneration [66,67]. Moreover, an improvement in clinical outcomes such as a 6-minute walk test and Minnesota Living with Heart Failure Questionnaire in cardiac patients receiving MSCs therapy was associated with increased LVEF [66,67].

Hare and co. conducted a randomized comparison on the safety and efficacy of allogeneic versus autologous BM-MSCs in patients with cardiomyopathy [57,68]. In both sorts of cardiomyopathies- ICM and DCM, transendocardial injections of allogeneic and autologous MSCs were equally safe without serious adverse events or immunological reactions, additionally propounding that allogeneic MSCs are characteristically immunomodulatory [57,68]. MSCs therapy improved the functional capacity and the quality of life in both clinical entities [57,68]. Several lines of evidence suggested clinically meaningful efficacy and immunosuppressive capacity of allogeneic MSCs compared to autologous MSCs in DCM patients [68]. Through endocrine or paracrine effects, which might promote neovascularization, inhibit cardiomyocyte apoptosis and enhance cardiac repair it is possible to explain the sustained improvement in LVEF, NYHA class, and myocardial perfusion [69]. Interestingly, ventricular remodeling was reversed by both of MSCs- autologous and allogeneic with inverse dose-response [57]. Specifically, in a group of patients with ICM who received lower-doses of MSCs (20 million cells) compared to the group that received 200 million cells, it was found that the first group of patients had significantly greater LVEF, improvement in LVESV, and a reduction in scar size [57]. Due to discrepant and conflicting results, Florea et al. evaluated the relationship between MSCs dose and clinical benefit in patients with ICM [70]. Although both cell doses (20 or 100 million allogeneic BM-MSCs) reduced the scar size, merely the higher dose of MSCs increased EF [70].

MSC-mediated modulation of peripheral artery disease

Peripheral arterial disease (PAD) is a common complication of atherosclerosis. One of the most severe forms of PAD is critical limb ischemia (CLI) which is characterized by rest pain, ischemic ulceration, or gangrene with or without tissue damage [71]. MSCs may improve the consequences of CLI due to their combining potential for inducing angiogenesis and the immunomodulatory environment in situ (Table 2).

During the 24-week follow-up period, the autologous transplantation of BM-MSCs in diabetic patients with CLI and foot ulcers was well tolerated and effective with respect to a few hemodynamic and clinical parameters [72]. In the same study, it was displayed that magnetic resonance angiography scores, Ankle-Brachial Pressure Index (ABPI), and transcutaneous oxygen pressure before and after the infusion of the cells revealed the increased blood flow, presumable interceded by collateral vessel development [72]. The clinical improvement was verified by ulcer healing rate and painless walking [72]. Posterior to intramuscular administration of allogeneic BM-MSCs (2 million cells/kg) in patients with CLI, significantly improved ankle pressure and ABPI were noticed [73]. There was no utility in the treatment with BM-MSCs for patients with impending amputation [73]. Due to the higher frequency of obtaining the unit of tissue per volume, and larger angiogenic potential compared to BM-MSCs, adipose tissue-derived MSCs (AT-MSCs) have been proposed as feasible approaches for the treatment of disorders related to limb ischemia [74]. A CellDREAM trial displayed that the intramuscular injection of AT-MSCs into the ischemic leg of patients with CLI improved ulcer evolution and wound healing and increased transcutaneous oxygen pressure without any further complications [74]. Besides, a meta-analysis on the usage of stem cell therapy in CLI certified the benefits observed in single studies [75].

Mesenchymal stem cells therapy in stroke

By using the conventional definition of stroke, it can be understood as the abrupt beginning of the loss of focal neurological function due to infarction or hemorrhage in the critical segment of the brain, retina, or spinal cord [76]. It is also important to note that stroke is the leading cause of major disabilities and the second leading cause of death worldwide [77]. Many studies revealed that the application of MSCs in ischemic stroke is secure [78-82], and effective throughout long-term tracking [78-80,82] (Table 2). In the first intracerebral stem cell transplantation study, 18 patients with chronic stroke received a single dose of modified BM-MSCs (SB623) (2.5×10^6, 5.0×10^6, or 10×10^6) and demonstrated a significant improvement in the neurological function measured by means of the European Stroke Scale (ESS), the National Institutes of Health Stroke Scale (NIHSS), Fugl-Meyer (F-M) total score, and Fugl-Meyer (F-M) motor function total score at 12 months after the treatment [78].

Lee and co. elucidated that the intravenous application of 5×10^7 autologous MSCs to patients with ischemic stroke improved the clinical parameters that were correlated with the plasma stromal cell-derived factor-1 alpha level at the time of MSC treatment as well as significantly reduced the mortality rate compared to a control group [82]. Levy and co. showed that the intravenous injection of allogeneic MSCs (the same as the autologous transplantation of MSCs) in patients with chronic stroke did not cause any adverse events [80]. MSCs in each dose (0.5, 1.0, and 1.5 million cells/kg body weight) were safe and related to the functional recovery [80].

Table 2. Clinical trials using MSCs in peripheral arterial disease and stroke therapies

Disease	Source of MSCs	Administration route	Dose (cell number x 10^6)	Follow-up period (months)	Outcome	Ref
CLI and foot ulcers	auto-BM-MSCs	IM	930	4	significant improvements in limb perfusion regarding painless walking time, ABI, TcO_2, and MRA, and promotion of foot ulcer healing	72
CLI	allo-BM-MSCs	IM	2/kg	24	improvement in rest pain, significant increase in ABPI and ankle pressure, healing of ulcers, and amputation rates	73
CLI	auto AT-MSCs	IM	100	6	TcO_2 increased, improvement in wound healing	74
chronic stroke	allo-BM-MSCs (SB623)	IC	2.5, 5.0, or 10	12	significant improvement in neurological function in ESS, NIHSS, F-M total score and F-M motor function total score	78
chronic stroke	allo-BM-MSCs	IV	0.5, 1.0, and 1.5/kg	12	significant improvements in NIHSS, BI, MMSE and GDSS	80
ischemic stroke	auto-BM-MSCs	IV	50	60	clinical improvement according to mRS, and level of SDF-1α	82

Abbreviations: CLI- critical limb ischemia; Auto- autologous; Allo- allogeneic; BM-MSCs- bone marrow-derived mesenchymal stem cells; AT-MSCs- adipose tissue-derived mesenchymal stem cells; IM- intramuscular injection; IV- intravenous injection; ABI- ankle-brachial index; TcO_2- transcutaneous oxygen pressure; MRA- magnetic resonance angiography; ABPI- Ankle Brachial Pressure Index; ESS- European Stroke Scale; NIHSS- National Institutes of Health Stroke Scale; F-M- Fugl-Meyer total score; mRS- modified Rankin Scale; SDF - 1α- Stromal Derived Factor 1-α; BI- Bartal score index; MMSE- Mini-Mental Status Exam; GDSS- Geriatric Depression Scale scores.

Conclusions

Mesenchymal stem cells are considered the new therapeutic agents in the treatment of CVDs, on the grounds of their differentiation abilities and paracrine effects. The results obtained in a large number of clinical trials suggest that the local as well as the systemic application of autologous or allogeneic MSCs is a beneficial therapeutic approach for CVDs. Although these studies are paving the way for the development of MSC-based regenerative therapies for structural and functional disorders of the myocardium and blood vessels, the optimal origin and the number of transplanted MSCs as well as the route of their application should be clearly defined and uniformed in such a way so as to increase the reproducibility and the consistency of the data. Moreover, safety issues regarding MSCs-based therapy are still a matter of debate. The primary concern is the unwanted differentiation of the transplanted MSCs and their potential to suppress the anti-tumor immune response and generate new blood vessels that may promote tumor growth and metastasis [83-86], although some studies displayed opposite results [86]. Therefore, new clinical studies should be focused on the continuous monitoring and the long-term follow-up of MSC-treated patients in order to determine the possible side effects of MSC-based therapy of CVDs.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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