

Stem cell therapy for dilated cardiomyopathy: systematic review of the existing data and ongoing trials

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Objectives

The aim of this review is to preview recent advances in clinical applications of stem cell therapy in nonischemic dilated cardiomyopathy (DCM).

Data sources

PubMed and OVID Library were searched. There was no restriction on the publication year. Articles in English language only were reviewed. Clinicaltrials.gov was searched also to find ongoing and unpublished trials.

Study selection

Studies that included adult DCM patients injected with any type of stem cells were selected. Data extraction: in this review, data from published studies were manually extracted and summarized.

Data synthesis

In this review, the data revealed that stem cell therapy can change the course of the disease through improving Left Ventricular Ejection Fraction (LVEF), New York Heart Association (NYHA) functional class, exercise tolerance, and quality of life of the patients.

Findings

The results of clinical trials in this field are encouraging, so DCM may be a more attractive target for stem cell therapy than chronic ischemic heart failure, where studies up till now failed to demonstrate a standardized result of treatment with stem cells on myocardial performance.

Conclusion

Stem cells have been considered in the treatment of DCM to improve myocardial performance, functional capacity, and neurohumoral activation; this may pave the way for more prevalent clinical use in DCM treatment. Future stem cell methods ought to aim for additional individual therapeutic approach by establishing the optimum stem cell type or their combination, dose, and delivery technique for each patient adjusted for the patient's age and stage of the disease.

Keywords:

clinical trials, dilated cardiomyopathy, stem cells

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Introduction

In spite of recent improvements in medical and device therapy, dilated cardiomyopathy (DCM) appears to be a widespread disease that costs the world a lot. The different treatment modalities for DCM aim to reduce hospital admissions due to heart failure, improve its symptoms and signs, and importantly improve patients' survival, but no therapeutic modality dealt with the repair of the diseased myocardium [1].

The first published successful experiment in the use of stem cells was done on mice. Bone marrow stem cells were transplanted in the infarcted myocardium of the mice to test whether the infarcted myocardium could be restored or not [2]. Another experiment on a rat model of DCM showed improved function of the cardiac muscle after transplantation of pluripotent mesenchymal stem cells (MSCs) [3]. Stem cell therapy in DCM has not the same growing steps as in chronic ischemic heart failure. Few clinical studies were performed to examine the effect of stem cells in DCM patients. In this review, we discuss the recent advances in stem cell treatment

in DCM, with a concentration on how to select the patient, type of stem cells, delivery route, and the effect of the treatment clinically and functionally. The aim of this review is to preview recent advances in clinical applications of stem cell therapy in nonischemic DCM.

Materials and methods

The full search strategy is provided in the Preferred Reporting Items for Systematic reviews and meta-analyses statement.

Data sources

The searched databases were PubMed and OVID libraries. The searched key words were DCM and stem

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cells. Articles in English language only were reviewed. We used articles published any year without restriction. Another search was done in clinicaltrials.gov to find ongoing and unpublished trials with the same criteria.

Study selection

Clinical, prospective, randomized trials with DCM adult patients (18 years or older) received any type of stem cells assessing the clinical and functional improvement of the patients with any follow-up period. Ongoing trials that were withdrawn or terminated before the enrollment were excluded. Papers selected for retrieval were assessed by an independent reviewer for methodological validity prior to inclusion in the review using standardized critical appraisal. Any disagreements that ascended between the reviewers were resolved through discussion.

Data extraction

Quantitative data were extracted from papers included in the review manually. The data extracted included explicit information about the types of stem cells, methods of delivery, and clinical and functional improvement.

Data synthesis

Qualitative research findings were pooled to measure the clinical and functional improvement in DCM patients through the changes occurring in left ventricular (LV) function, NYHA functional class, 6-min walk test (6MWT), quality of life (QOL), NT-proBNP, and major adverse cardiac event (MACE).

Results

Thirteen published trials that met our inclusion criteria were identified in our search and are analyzed in Table 1. The results of most trials revealed improvement in LVEF, exercise capacity, and functional status, which positively affects the lifestyle of the patients. These encouraging results make stem cell therapy an attractive line of treatment for patients with DCM, but needs more research as DCM has heterogeneous etiology. Stem cells have to be more specified in the type of cell, dose, and mode of cell delivery to each patient to guarantee effective and safe treatment.

The data from the unpublished ongoing trials are collected and analyzed in Table 2. The future results of these trials will offer more illustration of the role of stem cell therapy in this category of patients.

Discussion

This review aims to clarify the actual role of stem cell therapy in DCM patients. We focused in our review on parameters that are important in disease management. We emphasized on cell types and doses, patient selection, delivery methods, the change in NYHA functional classification, 6MWT (exercise capacity), QOL, and MACE. According to the published data, previous reviews mostly focused on LVEF and mortality end points only.

Stem cells have the ability to differentiate into several types of cells if moved out to other tissues. Bone marrow-derived stem cells [bone marrow mononuclear cells (BMMC)] are the most preferred for stem cell therapy studies as they are easily harvested. In both the ABCD trial [4] and the Bocchi *et al.* [5] study, intracoronary infusion of BMMC caused improvement in LVEF, NYHA functional class, and QOL. On the other hand, in IMPACT-DCM and Catheter-DCM studies (NCT00765518, NCT01020968), there was no significant improvement in DCM patients [9].

In more recent trials, REGENERATE-DCM (NCT01302171) [10] and INTRACELL trial (NCT00743639) [11], BMMC transplantation caused improvement in both clinical and functional status of the patients, while in the DCM arm of the Mi Heart study (NCT00333827) there were no considerable differences in the changes in LV function [12].

The DCM-SUPPORT study (NCT 03572660) is an active-phase II study that aims to test the effect of autologous BMMC and G-CSF on DCM. LVEF will be measured by computed tomography at 3 and 12 months. The change of NYHA functional class, exercise capacity, and MACE will be also assessed at 3 and 12 months. In another ongoing phase IIb clinical trial in Spain (NCT02033278), patients are randomized to receive IC injection of BMMC or placebo. During the 24 month follow-up period, LV function should be assessed by echocardiography and the change in NYHA functional class, NB-proBNP, and exercise tolerance.

By gathering these data, the results of these trials are found to be conflicting and this difference may be due to the various delivery methods, variation in BMMC dose, multiple methods of LV function assessment, or low statistical power.

MSCs can differentiate into cardiomyocytes and endothelial cells *in vitro*. The most characteristic feature of MSC is that they do not cause activation of the immune response. Clinical trials of MSC have

Table 1 Results of clinical trials of stem cell therapy in dilated cardiomyopathy

Trial name	Design	Study phase of LVEF evaluation	Patient number	Follow-up (months)	Cell type	Number of transplanted cells (in millions)	Delivery method	Primary and Secondary end points					
								LVEF	NYHA class	QOL	6MWT	NT-proBNP	MACE
ABCD (NCT unavailable) (2010) [4]	Prospective, randomized, open-label	II	81 (41 treated/40 control)	36	BMMC	168	IC	↑	↓	-	-	-	-
Bocchi <i>et al.</i> [5] (NCT unavailable)	Prospective, randomized, open-label	II	40 (23 treated/17 controls)	5	BMMC	Not available	IC	↑	↓	↑	-	↓	-
Vrtovec <i>et al.</i> [6] (NCT00629018)	Prospective, randomized, open-label	II	55 (28 treated/27 controls)	12	HSC (CD34+)	123±23	IC	↑	-	-	↑	↓	↓
Vrtovec <i>et al.</i> [7] (NCT01350310)	Prospective, randomized, open-label	II	110 (55 treated/55 controls)	60	HSC (CD34+)	113±26	IC	↑	-	-	↑	↓	↓
Vrtovec <i>et al.</i> [8] (NCT01350310)	Prospective, randomized, open-label	II	40 (20 IC injections/20 TE injections)	12	HSC (CD34+)	IC: 103±27 TE: 105±31	IC	↑	-	-	↑	↓	↓
IMPACT-DCM and Catheter-DCM (NCT00765518) [9]	Prospective, randomized, open-label	IIA	29 (18 treated/11 control)	6-12	ixmyelocel-T (from BMMCs)	35-295	TEP, TEC	NS	NS	NS	NS	NS	-
REGENERATE-DCM (NCT01302171) [10]	Prospective, randomized, placebo-controlled, double-blind	II	60 (15 peripheral G-CSF, 15 peripheral placebo, 15 IC stem cells, 15 IC serum)	12	BMMC	216±221	IC	↑	↓	↑	↑	↓	↓
INTRACELL (NCT00743639) [11]	Prospective, randomized, open-label	II	30 (20 treated/10 placebo)	12	BMMCs	106	TEP	↑by Echo Ns by MRI	↓	-	↑	-	-
Mi Heart (NCT00333827) (2015) [12]	Randomized, double blind, placebo control	II	160 (82 treated/78 placebo)	12	BMMCs	236	IC	NS	NS	NS	NS	NS	-
Butler <i>et al.</i> [13] (NCT02467387)	Prospective, randomized, single-blind, placebo controlled	II	22 (10 treated/12 placebo)	6	Allo-MSC	1.5 million cells/kg	IV	↑	↓	↑	↑	↓	NS
POSEIDON-DCM (NCT01392625) (2017) [14]	Prospective, randomized, open-label	I/II	37 (19 allo-MSC/18 auto-MSC)	12	Allo-MSC versus auto-MSC	100	TEC	↑	-	↑	↑	↓	-
RIMECARD Trial (NCT01739777) [15]	Prospective, randomized, double-blind, placebo-controlled	I/II	30 (15 treated/15 placebo)	12	Allogenic UC-MSCS	1×10 ⁶ UC-MSCs/kg	IV	↑	↓	↑	-	-	-
REMEDIMUM (NCT02248532) (2018) [16]	Prospective, randomized, double-blind	II	60 (30 repetitive cell therapy/30 single cell therapy)	6-12	CD34+	80	TEC	NS	NS	NS	NS	NS	-

6MWT, 6-min walk test; allo-MSC, allogeneic mesenchymal stem cells; auto-MSC, autologous mesenchymal stem cells; BMMC, bone marrow mononuclear cells; cCT, cardiac computed tomography; DCM, dilated cardiomyopathy; Echo, echocardiography; HSC, hematopoietic stem cells; IC, intracoronary route; IV, intravenous route; MACE, major adverse cardiac event; NS, nonspecific changes; SPECT, single-photon emission computed tomography; TEC, transcatheter route; TEP, transepical route; QOL, quality of life; UC-MSC, umbilical cord-derived mesenchymal stem cells.

Table 2 Ongoing trials of stem cell therapy in dilated cardiomyopathy

Study name (clinicaltrials.gov identifier)	Study type	Study phase	Patients enrolled	Key inclusion criteria	Cell type	Delivery route	Follow-up (months)	Enrollment status	Estimated completion date	Expected outcome measures
DYNAMIC (NCT02293603)	Randomized double-blind, placebo-control	Phase 1-2	42	On OMT, NYHA III-IV	Allogeneic CDC	IC	12	Active, not recruiting	April 2020	MACE and HF events
DCM-support (NCT 03572660)	Randomized single-blind	II	20	On OMT, NYHA III-IV	Allogeneic BMMSCs and G-CSF	IC	12	Not yet recruiting	July 30, 2021	LVEF and MACE and HF events
Infusion Intracoronary of Mononuclear Autologous Adult No Expanded Stem Cells of Bone Marrow on Functional Recovery in Patients with Idiopathic DCM and heart failure (NCT02033278)	Double-blind, randomized, controlled placebo	IIb	51	On OMT, NYHA II-IV	Autologous BMMSCs	IC	24	Recruiting	February 2022	LVEF angiographically and MACE and HF
DREAM-HF/TEVA (NCT02032004)	Randomized double-blind, sham-control	III	600 ischemic or nonischemic etiology	On OMT, NYHA II-III	Allogeneic-MSC	TEC	60	Recruiting	December 2019	MACEs and HF, 6MWT and LV volumes

6MWT, 6-min walk test; CDC, cardiosphere-derived cells; DCM, dilated cardiomyopathy; HF, heart failure; MACE, major adverse cardiac event; MSC, mesenchymal stem cell.

shown more encouraging results in DCM patients than BMMC [13,15]. Other trials also compared allogeneic-MS and autologous-MS [14]. Many strategies have been constructed to control the problem of the immune response as the use of immunosuppressant, HLA matching, genetic cell manipulation, and use of chemical or biomaterials for reducing the risk of immune recognition [17]. Currently active, ongoing phase III trial DREAM-HF (NCT02032004) tests the efficacy of transendocardial delivery of allogeneic-MS (Rexlemestrol-L) on heart failure patients by evaluating the changes in LV function, 6MWT, and MACE.

Hematopoietic stem cells (HSCs) are a good base for tissue neovascularization because they have the potential to differentiate into endothelial cells and are positive for the CD34+ surface marker. The procurement of HSC is more complex and has higher cost and so are not widely used in trials. The first clinical trial estimated the outcome of HSC in DCM was done by Vrtovec *et al.* [6]. After a 1-year follow up, the treated group showed increases in LVEF by 5%, an improvement in 6MWD and NT-proBNP levels and more importantly less 1-year mortality and heart transplantation. After that, the authors published the results of the long-term 5-year follow-up of patients who received CD34+ cell therapy. The improvement observed in the 1-year follow-up was persisted and confirmed in the 5-year follow-up period [7]. Then another paper was published comparing between transendocardial and intracoronary CD34+ transplantation in DCM patients and its results clarified that the transendocardial route is associated with more improvement in LV function, exercise tolerance, and NT-proBNP than the intracoronary route [8].

Recently, the REMEDIUM trial [16] (NCT02248532) evaluated the effect of repetitive transendocardial CD34+ injection in DCM, but the two groups did not show significant differences in change in LVEF or other physical or chemical parameters. More clinical trials are needed to prove this result or reject it.

Cardiosphere-derived cells (CDC) are obtained from the myocardial tissue. CDC can differentiate into cardiomyocytes *in vitro* but not tested *in vivo* in a complete clinical study yet. The DYNAMIC trial (NCT02293603) is an active, ongoing phase I clinical study that aims to test the safety and efficacy of IC allogeneic human CDC. Forty-two patients receive IC infusion of CAP-1002 or placebo. The treated group will receive multiple IC injections of CAP-1002. This study is done in the United States and is anticipated to end in April 2020 and its primary endpoint is unexpected death and MACE.

This review proves that stem cell therapy can be an attractive line of treatment in DCM as it causes improvement in both clinical and functional status of the patients and this is reflected in the lifestyle and care of the patients. Although autologous BMSC were the most used type in DCM clinical trials, the more differentiated types of cells showed more encouraging results. Research should be continued to determine which cell type is the most appropriate for cardiac regeneration in this category of patients after adequate testing *in vitro* and in preclinical studies. More studies with longer follow-up periods, more participants, more specified stem cell types, and better selection of the patients, according to the stage and etiology of the disease are needed.

Conclusion

The currently published clinical trials in the issue of stem cell therapy in DCM offer encouraging data about this treatment. The results of these clinical trials showed improvements in LV function, exercise capacity, functional status, and MACE. Larger clinical trials in this field with longer follow-up periods are mandatory to confirm the results of the previous trials, and to cover up the weakness points considering more personalized stem cell therapy for each patient according to clinical status, stage of the disease, and preexisting comorbidities.

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Conflicts of interest

There are no conflicts of interest.

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