Cell Therapy, a Novel Remedy for Dilated Cardiomyopathy? A Systematic Review

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ABSTRACT

Background: Dilated cardiomyopathy (DCM) is the most common form of nonischemic cardiomyopathy worldwide and can lead to sudden cardiac death and heart failure. Despite ongoing advances made in the treatment of DCM, improvement of outcome remains problematic. Stem cell therapy has been extensively studied in preclinical and clinical models of ischemic heart disease, showing potential benefit. DCM is associated with a major health burden, and few studies have been performed on cell therapy for DCM. In this systematic review we aimed to provide an overview of preclinical and clinical studies performed on cell therapy for DCM.

Methods and Results: A systematic search, critical appraisal, and summarized outcomes are presented. In total, 29 preclinical and 15 clinical studies were included. Methodologic quality of reported studies in general was low based on the Centre for Evidence Based Medicine, Oxford University, criteria. A large heterogeneity in inclusion criteria, procedural characteristics, and outcome measures was noted. The majority of studies showed a significant increase in left ventricular ejection fraction after cell therapy during follow-up.

Conclusions: Stem cell therapy has shown moderate but significant effects in clinical trials for ischemic heart disease, but it remains to be determined if we can extrapolate these results to DCM patients. There is a need for methodologically sound studies to elucidate underlying mechanisms and translate those into improved therapy for clinical practice. To validate safety and efficacy of cell therapy for DCM, adequate randomized (placebo) controlled trials using different strategies are mandatory. (*J Cardiac Fail 2013;19:494–502*)

Key Words: DCM, nonischemic cardiomyopathy, heart failure, stem cells.

Dilated cardiomyopathy (DCM) is the most common form of nonischemic cardiomyopathy worldwide.[1] Estimated prevalence in adults is 1/2,500 individuals, with an incidence of 7/100,000 per year. It is defined by dilation and impaired contraction of heart muscle in the absence of an obvious etiology such as ischemic heart disease or valve disease. Causes are multifactorial, including genetics as a major contributor. DCM can lead to sudden cardiac death and heart failure, and carries a heavy burden on health care resources owing to a high rate of hospital admission and occasional need for ventricular assist device and/or heart transplantation. Over the past years, progress has been made in treating DCM, but improving outcome remains a difficult goal to achieve.

Stem cell therapy for cardiac repair has been extensively studied in acute myocardial infarction and chronic ischemic

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heart disease, showing potential benefit.[2–4] Proposed working mechanisms include, e.g., transdifferentiation of stem cells to cardiomyocytes, activation of intrinsic cardiac stem cells, paracrine effects, and angiogenesis. Only a few studies have been reported on cell therapy for DCM, with human trials since 2006. To the best of our knowledge, no complete overview has been reported so far. In the present systematic review, preclinical and clinical studies on cell therapy for DCM are reported, including validity, procedural characteristics, safety, and outcome measures.

Methods

Data Collection and Analysis

We searched PubMed and Embase for reports of preclinical (all years) and clinical (2006−2012) therapeutic studies on various types of cell therapy for nonischemic DCM (search syntaxes are provided in Supplemental Tables 1 and 2). To prevent selection and retrieval bias, outcome was not included in the search syntaxes. Only English- and German-language articles were included, and no restrictions were imposed on timing of assessment and follow-up. Excluded were abstracts, reviews, reports from scientific sessions and discussions, case reports, in vitro studies, studies only on ischemic heart disease, pediatric studies, and articles describing study design. Retrieved studies were used for cross-reference checking and carefully examined to exclude potentially duplicate or overlapping data. Reviews and case reports were available for background information. A separate search was performed on ClinicalTrials.gov for ongoing trials (Supplemental Table 3). Authors were contacted for missing data.

Assessment of Quality and Risk of Bias

For assessment of quality, risk of bias (e.g., selection or information bias), and heterogeneity, remaining articles were considered for critical appraisal. Quality of studies were assessed in duplicate (by G.K. and J.G.) with the use of standard forms for relevance and validity according to the Centre for Evidence Based Medicine, Oxford University, criteria.[5] Study design was determined, and adequate randomization (concealed allocation) or comparable groups when not randomized, losses to follow-up, and blinding of physician/treatment officer or researcher were reviewed.

Data Extraction and Management

Study characteristics and used outcome measures were summarized. If necessary, data were estimated graphically or calculated with standard deviations from available data with the use of SPSS 17.0 (Chicago, Illinois). Two-tailed P values $<.05$ were considered to be significant.

Results

Preclinical Studies

Literature Search. Our preclinical search yielded 1,455 unique articles (Fig. 1). After screening of title and abstract with the use of inclusion and exclusion criteria, 29 relevant articles remained; reference checking retrieved no new articles.

Study Characteristics and Quality Assessment. Quality assessment of included studies is presented in Supplemental Table 4. In summary, about one-half (15/29) were conducted in a randomized fashion; 1 study (Jin et al.) reported allocation concealment.[6] One study reported blinding of the treatment officer.[7] Twelve studies reported blinding of the effect investigators for treatment. All relevant data of the 29 studies are presented in Table 1. Two studies used a large animal model (Hata et al: dogs; Psaltis et al: sheep); all other studies used rodent or rabbit models. Delivery route varied between intracoronary or intravenous infusion, intramuscular injection, sheet graft, or surgical injections, and in total 10 different stem cell types were used. Fractional shortening, fractional area change, and ejection fraction were determined by 2-dimensional echocardiography in almost all of the studies; only Psaltis et al used magnetic resonance imaging (MRI) to determine ejection fraction. Delta pressure/delta time and peak systolic pressure were measured with the use of hemodynamic measurements. Five studies reported baseline data, showing no significant differences in the study groups. Twenty-one out of 29 studies had sufficient and comparable proportions of follow-up, and length of follow-up varied from 2 to 21 weeks. Lin et al, Sun et al, and Kondoh et al (2006 and 2007) reported interim results on ejection fraction or fractional shortening. Most studies (24/29) used comparable treatment methods between control and therapy groups. Eighteen out of 29 studies (62%) were published in a journal with impact factor ≥3.00.

Efficacy and Safety in Animal Models. All animal studies demonstrated a positive effect of stem cell therapy on left ventricular function, of which 24 studies showed significant improvement, ranging from 3.0% to 24% on echocardiographic evaluation (Table 1). In general, no safety issues were found in these studies. Of 18 studies that assessed mortality, 3 found improvement in survival.[8–10] Ten studies found equal mortality between treatment and control groups, other studies did not mention significance, and no cardiac tamponade was reported. Four studies detected no arrhythmias; other studies did not mention any occurrence of arrhythmias.[10–13]

Clinical Studies

Literature Search. Our clinical search strategy yielded 339 unique hits (Fig. 2). Screening of title and abstract using inclusion and exclusion criteria resulted in 16 relevant articles. One relevant peer-reviewed article was found not indexed on PubMed or Embase.[14] All principle investigators from ongoing trials were contacted for up-to-date trial results (see Ongoing Clinical Trials, below), this resulted in 2 additional complete manuscripts.[15,16] Reference checking retrieved no new articles. Four articles were excluded because of overlapping data. In total, 15 articles were considered for critical appraisal (4 randomized controlled trials [RCTs], 2 non-RCTs, 9 cohort studies).

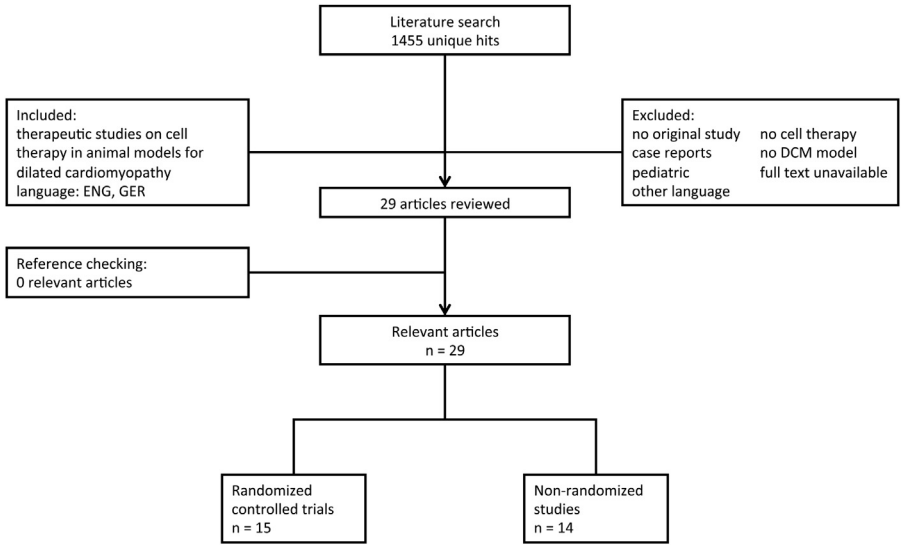

Fig. 1. Flowchart of search strategy preclinical studies. ENG, English; GER, German; DCM, dilated cardiomyopathy.

Authors were contacted for articles not available in full text and missing data (8 authors responded).

Study Characteristics and Quality Assessment. Four out of 15 studies were randomized; 2 nonRCTs used matched control groups (Table 2). Supplemental Table 5 presents further methodologic quality of the included studies. Allocation concealment was not reported in the RCTs. There was no patient or physician blinding performed in these clinical studies, nor placebo used in the controlled trials. Two of the controlled trials described equally treated groups aside from the allocated treatment.[17,18] Losses to follow-up were reported and adequate (≤20%) in 13 out of 15 studies. All articles were published in peer-reviewed journals, 5 (33%) of the 15 studies in a journal with impact factor ≥3.00.

Sample size ranged from 3 to 131 persons and overall follow-up duration from 3 to 60 months. Definitions used for dilated cardiomyopathy were different between studies. Seven studies reported excluding patients with coronary artery disease on coronary angiography.[14,16,18–22] Only Schannwell et al performed endomyocardial biopsy in all patients to exclude myocarditis; Seth et al performed biopsies in 8/85 patients. Three studies included patients with ischemic cardiomyopathy in a separate group; those subgroups were excluded for this review.[14,23,24] For Fatkhutdinov et al, the groups undergoing concomitant (valve) surgery also were excluded. For cell delivery, the majority used an intracoronary route versus a surgical procedure with intramyocardial injections (11 vs 4). Cell type was different between studies: Mostly bone marrow stem cells were used; 2 studies used fetal material. Kirillov et al had 1 group with prenatal allogenic skeletal myoblasts and 1 with prenatal mesenchymal stem cells.[25]

Efficacy Outcomes in Clinical Trials. Main outcomes reported in clinical trials were left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, quality of life (QoL), and mortality. All but 1 article mainly used 2-dimensional echocardiography for determining ejection fraction; Fischer-Rasokat et al used angiography.[26] Cardiac MRI was only used in certain subgroups. Mean differences in LVEF between baseline and final follow-up values are presented in Table 2 (baseline and final LVEF values are presented in Supplemental Table 6). LVEF values were calculated for Argüero et al from available patient data; LVEF was estimated in the therapy groups of Fatkhutdinov et al and the control groups of Vrtovec et al (2011 and 2013), because these were only graphically depicted. The majority of studies (10/15) showed a significant increase in LVEF in the therapy group (range 3.2% to 11%). Four studies found no significant difference between baseline and follow-up in the therapy groups.[17,20,24,25] Kalil et al showed a significant decrease of 0.5% ($P = .023$) in mean ejection fraction at final follow-up (12 mo); in that study, LVEF increased in the first 2 months after surgical cell therapy but decreased afterward. In the control groups, increase of mean LVEF from baseline was less or LVEF decreased (range from about −5% to 5.6%). The highest increase was found in the control group of Bocchi et al, which underwent granulocyte colony−stimulating factor administration. Seth et al showed a significant difference ($P < .05$) between therapy and control groups (LVEF 5.9% vs 0.4%), and Vrtovec et al found a significant change in LVEF mean difference in both studies.[15,21,22]

NYHA functional class improved in all 9 studies that reported functional class, with significant improvements in more than one-half of them.[14,17,19,20,27] QoL was determined with the use of questionnaires and reported to be significantly improved in 6 studies.[14,19–21,27,28] Fatkhutdinov et al found an improvement in QoL at 3 months during

Table 1. Preclinical Study Characteristics and Outcomes

Author	Model	n (Total/Cell Treated)	Randomized	Follow-Up (wk)	Cell Type	Outcome	Measuring Method	Measured Effect	*P* Value
Large animals									
Hata (2006)[29]	4	12/5	No	4	MB	EF	CT, abs	+6.5%	<.05
Psaltis (2010)[30]	3	15/7	Yes	8	MPC	EF*	CT, abs	+10%	<.05
Small animals									
Baba (2007)[11]	3	67/20	No	4	ES	dP/dt	CT, rel	+27%/−20%§	"significant"
Chen (2006)[13]	3	24/8	No	4	BMMC	EF	CT, abs	+11.1%	<.05
Chen (2010)[41]	3	19/6	Yes	4	BM-MSC	EF	CT, abs	+6.4%	<.05
de Angelis (2010)[8]	3	160/?	No	6	CPC	EF	CT, abs	~+24%‖	<.05
Dhein (2006)[7]	3	38/14	Yes	4	BM-MSC	dP/dt	CT, rel	+62%/−88%§	<.05
Garbade (2009)[42]	3	31/15	No	4	BMMC	FS	CT, abs	+3%	<.01
Ishida (2004)[43]	3	52/18	Yes	4	BMMC	FS	CT, abs	+4.1%	ns
Jin (2010)[6]	3	20/10	Yes	4	BMMC	dP/dt	CT, rel	+35%/−32%§	<.05
Kondoh (2006)[9]	5	85/57	Yes	12	MB	FS	CT, abs	~+5%‖	<.05
Kondoh (2007)[44]	5	100/24	Yes	8	MB	FS	CT, rel	+31%	ns
Lin (2010)[45]	1	40/8	Yes	13	ADMSC	EF	CT, abs	+4.1%	<.0001
Lu (2006)[46]	3	35/18	Yes	4	BMMC	EF	CT, abs	+11%	<.05
Mu (2011)[47]	3	120/40	Yes	4	BM-MSC	dP/dt	CT, rel	+32%/−18%§	<.05
Nagaya (2005)[48]	1	30/10	No	4	MSC	FS	CT, abs	~+11%‖	<.05
Nakajima (2008)[49]	3	25/16	No	4	BMMC	FS	BF, abs	+3.1%	<.05
Nomura (2006)[50]	2	?/15	No	4	MDPC	FS	CT, abs	~+5%‖	<.05
Ohno (2002)[51]	2	41/11	No	5	MB	PSP	CT, abs	~+68%†,‖	<.001
Pouly (2004)[52]	2	26/14	Yes	4	MB	FAC	BF, rel	+24%	.019
Shabbir (2009)[53]	2	33/15	No	4	MSC	FS	CT, abs	~+13%‖	<.001
Singla (2012)[54]	3	?/?‡	No	2	CM or ES	FS	CT, abs	+5%	<.05
Sun (2009)[55]	1	28/10	Yes	13	BMMC	EF	CT, abs	+5.5%	.0002
Suzuki (2001)[56]	3	16/8	No	4	MB	dP/dt	CT, rel	+20%/−20%§	.01
Tezuka (2008)[12]	2	?/?	No	15	MB	dP/dt	CT, rel	+15%/−37%§	<.05
Werner (2005)[57]	1	25/12	No	4	EPC	FS	BF, rel	+15%	Unknown
Yamada (2008)[10]	6	118/8	Yes	21	ES	FS	BF, abs	+12.5%	<.05
Zhang (2005)[58]	3	42/18	Yes	4	BMMC	FS	CT, abs	+3.8%	ns
Zhou (2007)[59]	3	20/10	Yes	12	BMMC	EF	CT, abs	+0.1%	ns

Disease model: 1) porcine myosin + Freund adjuvant; 2) genetic δ-sarcoglycan deficiency; 3) doxorubicin or adriamycin; 4) pacing-induced DCM (230/min); 5) BIO TO-2 hamsters; 6) Kir 6.2 knockout + aortic constriction. Cell type: ADMSC, adipose-derived stem cells; BM(M)C, bone marrow (mononuclear) cells; CM, conditioned medium; CPC, cardiac progenitor cells; EPC, endothelial progenitor cells; ES, embryonic stem cells; MB, myoblasts; MDPC, myosphere-derived progenitor cell; MPC, mesenchymal precursor cells; MSC, mesenchymal stem cells. Measuring method: BF, baseline vs follow-up; CT, control vs therapy; abs, absolute difference; rel, relative difference. EF, ejection fraction; dP/dt, delta pressure/delta time; FS, fractional shortening; FAC, fractional area change; PSP, peak systolic pressure; ns, nonsignificant.

*Determined with the use of MRI.

†Average difference in PSP.

‡Singla used 6−8 animals per group; 1 group underwent cell therapy.

§Measured effect of dP/dt (maximum/minimum).

‖Estimated effect based on graphics.

follow-up, but at final follow-up the difference was nonsignificant.

Safety Outcomes in Clinical Trials. Mortality was reported in all studies except Bocchi et al. Comparing therapy and control groups, Vrtovec et al (2011) found a significantly lower incidence of heart transplantation or mortality in the therapy group (7% vs 30%; $P = .03$). At 5-year follow-up, Vrtovec et al (2013) found a lower total mortality in patients receiving stem cell therapy compared with control subjects (14% vs 35%; $P = .01$); occurrence of heart transplantation did not differ between the 2 groups. The other controlled studies found similar mortality rates. Chin et al, Fatkhutdinov et al, and Schannwell et al found no mortality in both groups, and of the 85 patients included by Seth et al 12 treated patients vs 14 control subjects had died after 3 years of follow-up. In the study by Argüero et al, which mainly included patients with ischemic cardiomyopathy, 2 patients died because of intractable arrhythmias, but there was no information given of which group either of these patients belonged to. Benetti et al, Kalil et al, and Martino et al reported some cases with de novo (supra)ventricular arrhythmias, quickly terminated with chemical or electrical cardioversion. The other studies did not show an increase in arrhythmias (only Seth et al gave no information on occurrence of arrhythmias).

Discussion

In total, 29 preclinical and 15 clinical studies were included in this systematic review on cell therapy for DCM. Main findings were: 1) a low methodologic quality in general; 2) a large heterogeneity in inclusion criteria, procedural characteristics, and outcome measures; 3) only 2 preclinical studies involving large animals; 4) a significant increase in LVEF, improvement in NYHA functional class, and QoL at follow-up after cell therapy in the majority of clinical studies (from a total of 513 enrolled patients); 5) several reports of potentially life-threatening arrhythmias; and 6) no increased mortality after cell therapy.

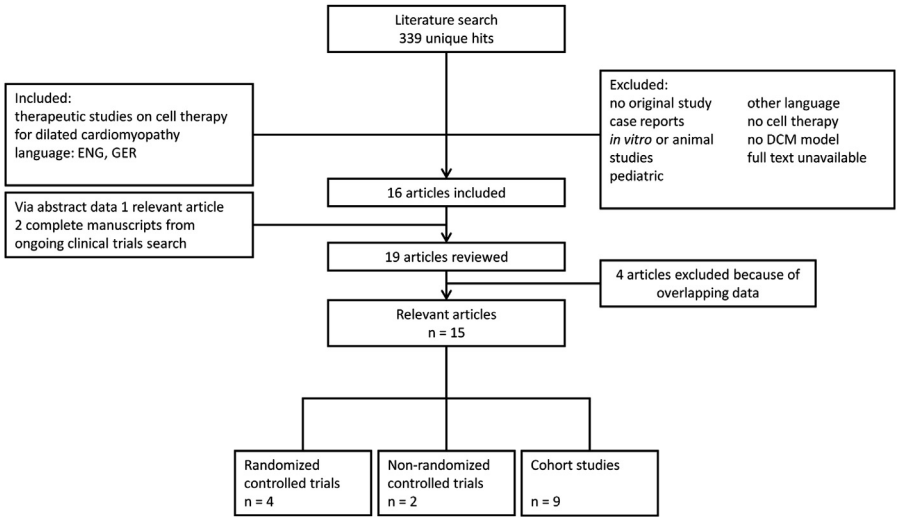

Fig. 2. Flowchart of search strategy clinical trials. Abbreviations as in Fig. 1.

From "Bench to Bedside"

Study validity in preclinical studies showed a lack in methodologic quality, about one-half were randomized, and only 1 study used concealed allocation. No blinding was performed in the majority of the included articles. We found a large heterogeneity among studies in disease models, therapy, and end points. It is therefore difficult to combine the results to infer a stronger conclusion on stem cell therapy. However, all studies showed a positive effect on left ventricular function, mostly by attenuation of deterioration, also shown in the studies reporting interim results (Fig. 3). Largest improvement was found by de Angelis et al using cardiac progenitor cells on doxorubicin-induced cardiomyopathy in rats. Contractility also was

Table 2. Clinical Study Characteristics and Outcomes

Author (year)	Group	n (total)	Follow-Up (mo)	Delivery Route	Cell Type	EF Mean Difference (%)	*P* Value
RCTs							
Bocchi (2010)[27]	Therapy	14 (23)*	±15†	IC	BMC	+8.8	.016
	Control	8				+5.6	.04
Seth (2010)[21]	Therapy	44 (85)	36	IC	BMC	+5.9	<.05
	Control	41				+0.4	ns
Vrtovec (2011)[22]	Therapy	28 (61)‡	12	IC	Autologous CD34+	+4.6	.03
	Control	27				~−2‖	Unknown
Vrtovec (2013)[15]	Therapy	55 (131)‡	60	IC	Autologous CD34+	+5.7	.02
	Control	55				~−3‖	Unknown
Non-RCTs							
Fatkhutdinov (2010)[17]	Therapy	6 (14)	12	IC	Allogenic MSC	~0‖	ns
	Control	8				~−5‖	ns
Schannwell (2008)[18]	Therapy	10 (20)	3	IC	BMC-MN	+9	<.01
	Control	10				0	ns
Cohort							
Argüero (2006)[23]		3 (5)§	Unknown	Surgical	Autologous CD34+	+8.7	.0059
Benetti (2010)[19]		10	40	Surgical	HFDSC	+8.2	.005
Chin (2011)[24]		3	12	IC	BM-MSC	+15.1	ns
Fischer-Rasokat (2009)[26]		33	12	IC	BMC	+3.2	<.001
Kalil (2008)[28]		9	12	Surgical	BMC	−0.5	.023
Kirillov (2007)[25]	Group 1	9	6	IC	Prenatal ASM	+2	ns
	Group 2	7			Prenatal MSC	+1.6	ns
Martino (2010)[20]		24	6	IC	BMC-MN	+1.2	ns
Ruengsakulrach (2011)[14]		52	±13†	Surgical	ACP	+4.4	.03
Suárez de Lezo (2013)[16]		27	12	IC	BMMC	+11	.001

RCT, randomized controlled trial; Cohort, cohort study. Cell type: ACP, angiogenic cell precursors; ASM, allogenic skeletal myoblasts; BM(M)C, bone marrow (mononuclear) cells; HFDSC, human fetal-derived stem cells; MSC, mesenchymal stem cell; MN, mononuclear; EF, ejection fraction; G-CSF, granulocyte colony−stimulating factor; IC, intracoronary; ns, nonsignificant.

*Randomized to G-CSF administration (14) or G-CSF associated to BMSC intracoronary infusion (8).

†Bocchi et al mean 468 ± 374 days (up to 1,190 days), Ruengsakulrach et al mean 409.7 ± 352.4 days.

‡All patients received G-CSF before randomization; 6 (2011) and 21 (2013) patients were excluded in this phase.

§3/5 patients included in preliminary report, outcomes calculated.

‖Estimated difference based on graphics.

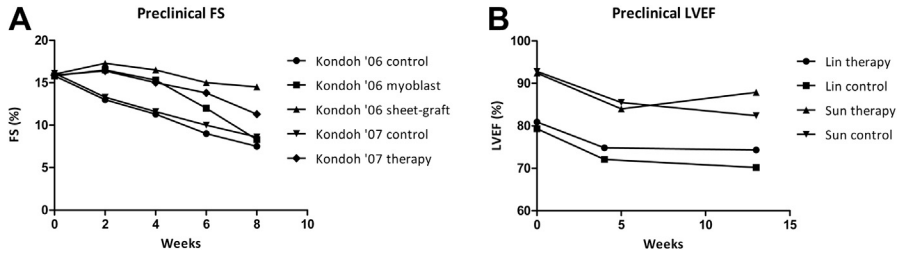

Fig. 3. Preclinical studies reporting interim results on (A) fractional shortening (FS) or (B) left ventricular ejection fraction (LVEF).

significantly and positively influenced. Comparing stem cell−treated animals with control animals, 10 out of 29 studies reported equal mortality or sometimes even improvement of survival. No conclusion can be drawn regarding arrhythmias, which was reported in only 4 studies.

Main proposed mechanisms of stem cell effects on DCM include reduction of fibrosis and angiogenesis by direct (cell engraftment, regenerative transdifferentiation) and paracrine support.[29,30] No additional fibrosis is seen following therapy; sometimes even attenuation is seen. It remains possible that publication bias and methods of measurement attributed an overestimation and positive image of stem cell therapy for DCM. Left ventricular hemodynamics and MRI are more objective than 2-dimensional echocardiography in measuring left ventricular function. An optimal animal model for DCM is still lacking. Overall, stem cell therapy seems to be feasible and effective in preclinical models; however, large animal studies are scarce in the transition from bench to bedside.

Back from ''Bedside to Bench''

Quality Assessment, Safety, and Efficacy in Clinical Trials. In 2006 consensus of the Task Force of the European Society of Cardiology (ESC) addressed the possible need for autologous cell therapy in DCM.[31] In the same year, the first human clinical trials were reported, and in summary they were predominantly pioneering trials assessing safety and efficacy. There was a lack in methodologic quality, because mainly nonrandomized trials were performed. Lack of allocation concealment, placebo effect, or procedural characteristics, such as delivery techniques and growth factor administration, could have influenced the outcome. Especially studies with a short follow-up period should be interpreted with caution regarding whether the positive outcome would be sustained over a longer period. We noticed a large heterogeneity in inclusion criteria, procedural characteristics, and outcome measures.

These studies showed no increase in mortality in the cell therapy groups. There were several reports on potentially life-threatening arrhythmias.[19,20,23,28] Furthermore, a case report (n = 2) describing a pilot trial on cell therapy in DCM showed severe complications after intracoronary balloon inflation, with hypotension and ventricular arrhythmias in one patient and severe spasm with hypotension requiring bailout stenting in another; therefore, that trial was prematurely terminated.[32] So these procedures carry an arrhythmic risk, which should be assessed in future studies.

There seems to be a positive effect of cell therapy for DCM on LVEF, NYHA functional class and QoL, although this should be verified in large randomized trials. Also, more studies are needed for determining optimal delivery route and cell type for cardiac repair. Outcomes should be given as absolute differences to more accurately estimate actual treatment effect. This would result in clear indications for cell therapy in nonischemic cardiomyopathy, preferable above random patient selection. Using multiple ''rising'' imaging modalities, such as MRI, 3-dimensional echocardiography, and single-photon emission computed tomography, would provide more accuracy for determining outcomes.[33] Although we would prefer MRI to determine outcome measures, certain heart failure patients would be ineligible because of implanted devices, such as implantable cardioverter-defibrillator and cardiac resynchronization therapy. Besides clinically relevant LVEF measurements, detailed measuring of local cardiac function can provide information about local changes induced by cardiac regenerative therapy.[34] Combined global and regional myocardial function measurements are recommended to assess the effects of cardiac regenerative therapy.

Elucidating Underlying Mechanisms. Current evidence reveals controversy regarding stem cell transdifferentiation to cardiomyocytes contributing to cardiac functional gain, which has led to investigating paracrine mechanisms for repair.[35,36] In contrast to cell therapy for ischemic cardiomyopathy, where angiogenesis plays an important role, in DCM heart muscle disease and myocardial dysfunction present a different background. However, marked vascular derangements and impaired vasculogenic and angiogenic responses have also been reported in idiopathic DCM.[37] Proposed underlying working mechanisms should be differentiated between ischemic cardiomyopathy and DCM, e.g., by elucidating these issues in preclinical studies. Findings from clinical studies should also be clarified in collaboration with preclinical research. As progress is being made for DCM in unraveling underlying genetic mutations and molecular mechanisms (e.g., calcium metabolism), these could be used in future for tailored cell and/or gene therapy.[38,39]

Ongoing Clinical Trials

Several clinical trials on cell therapy for DCM are underway (Table 3). Nine trials were found on ClinicalTrials.gov (Supplemental Table 3). All principle investigators were

Table 3. Ongoing Clinical Trials on Cell Therapy for Dilated Cardiomyopathy

Identifier (Short Name)	Design	Blinding	Delivery Route	Cell Type	Primary Outcome Measure (modality)	Estimated Completion Date	Status
NCT01302171 (REGENERATE-DCM)	RCT	Double-blind	IC	BM-MNC vs placebo/G-CSF	LVEF (MRI)	Dec 2012	Recruiting
NCT01350310 (NOGA-DCM)	RCT	Single-blind	IC vs IM	CD34+	LVEF (echocardiography)	Mar 2013	Recruiting
NCT00765518 (IMPACT-DCM)	RCT	Open-label	IM	CRC	Safety	Feb 2012	Completed
NCT01392625 (POSEIDON-DCM)	RCT	Open-label	TE	Autologous vs allogenic MSC	Safety	Jul 2015	Recruiting
NCT01020968	RCT	Open-label	TE	CRC	Safety	Feb 2012	Active, not recruiting
NCT00333827 (MiHeart)	RCT	Double-blind	IC	BMC	LVEF	Feb 2009	Unknown
NCT00721045 (Revascor)	RCT	Single-blind	TE	MPC	Safety	Jul 2011	Unknown

RCT, randomized controlled trial; IC, intracoronary; IM, intramyocardial; TE, transendocardial; BM-MNC, bone marrow mononuclear cells; G-CSF, granulocyte colony−stimulating factor; CRC, cardiac repair cells; BMC, bone marrow cells; MPC, mesynchymal precursor cells; MSC, mesenchymal stem cells; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging.

contacted for up-to-date trial results, which resulted in 2 complete manuscripts that were added to the clinical studies section. Most studies are randomized; only 1 study is double-blind and placebo controlled with another control group receiving granulocyte colony−stimulating factor. Delivery routes are intracoronary, intramyocardial, or transendocardial (mainly using the NOGA XP/Myostar injection catheter system), and different cell types are used. Primary outcome measures are assessing safety or LVEF.

Study Limitations

The large heterogeneity in study characteristics of included reports could have influenced outcome; therefore, we examined reasons for heterogeneity with the use of standardized criteria. Differences between animal DCM models and human disease carry limitations when translating from bench to bedside. Publication bias can not be ruled out, because smaller studies are prone to publication bias. Estimates of effect are vulnerable to confounding by lack of randomization. Only reported outcomes were included, because we did not have access to complete individual data and accordingly, mean values are provided; authors were contacted in case of missing data.

Future Implications

Only a few studies on cell therapy for DCM have been performed and methodologic quality in general was low. The majority of studies show a significant positive effect on LVEF. There is a need for methodologically sound (pre)clinical studies to elucidate underlying mechanisms and to translate these into improved therapy for clinical practice. Clearly described uniform definitions for inclusion should be used in future studies, e.g., derived from the ESC classification.[40] Adequately randomized (placebo) controlled trials are mandatory to validate safety and efficacy of cell therapy for DCM, preferably with long-term follow-up. These studies should focus on occurrence of arrhythmias, mortality, optimal cell delivery techniques, and cell type with the use of different modern image modalities. Stem cell therapy has shown moderate but significant effects in clinical trials for ischemic heart disease comprising almost 2,000 patients.[4] It still remains to be determined if we can extrapolate these results to DCM patients. Nevertheless, this exciting field of research has shown promising results so far and warrants continuation of ongoing study programs.

Disclosures

None.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cardfail.2013.05.006.

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