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Clinical cell-based cardiac regeneration therapy in patients with ischemic heart failure

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Since the number of the autologous remnant cardiac progenitor cells and the mobilized cells form the bone marrow upon injury signal are too low, as well as the own myocyte proliferation rate is insufficient for complete recovery of the heart after ischemic injury, external regenerative cells are implanted into the injured heart to promote the regeneration process. Accordingly, the clinical cardiac regeneration treatment with the intention to improve clinical symptoms, quality of life, and LV performance, as well as prevention of hospitalization, reduction of mortality and morbidity came into the forefront of pre-clinical and clinical investigations in the last 15 years. The majority of the heart failure clinical cell-based cardiac regeneration studies included patients with low ejection fraction (<40%), and applied the cells (mostly bone-marrow, or mesenchymal stem cells) percutaneously intramyocardially. Most studies and meta-analyses resulted in moderate improvement of the left ventricular function and quality of life, however, the last three randomized trials failed to reach the primary efficacy endpoints. To enhance the effectiveness of the regeneration therapy in heart failure, cell-free therapy with paracrine factors, including exosomes and cell function modulators, such as noncoding RNAs came into foreground.

Keywords: heart failure, cell-based cardiac regeneration therapy, cell-free therapy, clinical studies

Klinikai sejtalapú kardiális regenerációs kezelés az iszkémiás szívelégtelenségben szenvedö betegekben

Ismert, hogy az autológ kardiális progenitor sejtek és a myocadium sérülés hatására a csontvelőből mobilizált sejtek száma túl alacsony és a cardiomyocyták saját proliferációs képessége nem elegendő a szív iszkémiás károsodásának teljes regenerálásához. Teoretikusan, reparatíve sejtek sérült myocardiumba való implantálása elösegítheti a regeneráció folyamatát. Ennek megfelelően az elmúlt 15 évben a klinikai tünetek, az életminőség és a balkamra-funkció javítását, a hospitalizáció megelőzését és a mortalitás valamint a morbiditás csökkentését célzó kardiális regenerációs kezelés a preklinikai és klinikai vizsgálatok élvonalába került. A szívelégtelenségben végzett sejtalapú, klinikai, kardiális regenerációs vizsgálatok többségében alacsony bal kamra ejekciós frakciójú (LVEF<40%) betegek kerültek besorolásra és az alkalmazott sejtek elsősorban csontvelői eredetű, vagy mesechymalis őssejtek voltak, amelyeket percutan intramyocardialisan alkalmaztak. A legtöbb vizsgálat és metaanalízis a balkamra-funkció és az életminőség mérsékelt javulását mutatta, a legutóbbi három randomizált vizsgálat azonban nem igazolt kedvező változást a primer effektivitási végpontokat illetően. Szívelégtelenségben a regenerációs terápia hatásosságának javítása céljából a sejtmentes kezelési alternatívák, így parakrin faktorok többek között exosomák, sejtfunkció-modulátorok pl. nem kódoló RNS-ek alkalmazása került előtérbe.

Kulcsszavak: szívelégtelenség, sejtalapú kardiális regenerációs kezelés, sejt-mentes regenerációs terápia, klinikai vizsgálat

Introduction

The incidence of ischemic heart failure (HF) caused by coronary artery disease (CAD) is increasing due to successful reduction of acute complications of myocardial infarction and improved survival. Those patients are typically left with reduced left ventricular (LV) with subsequent chronic heart failure symptoms. The available therapeutic options are limited to medical treatment to improve their symptoms, apart from device therapy/heart transplantation in serious cases. Since the number of the autologous remnant cardiac progenitor cells and the mobilized cells form the bone marrow upon injury signal are too low, as well as the own myocyte proliferation rate is insufficient for complete recovery of the heart after ischemic injury, external regenerative cells are implanted into the injured heart to promote the regeneration process. Accordingly, the cardiac regeneration treatment with the intention to improve clinical symptoms, quality of life, and LV performance, as well as prevention of hospitalization, reduction of mortality and morbidity came into the forefront of pre-clinical and clinical investigations in the last 15 years.

Cells used for cardiac regeneration in ischemic HF

At the beginning of the cell-based regenerative therapy, unselected mixed cells of bone marrow origin were used in clinical trials for cardiac repair, because of a lack of information about which cell type would be best suited. Most bone marrow cells belong to hematopoietic and lymphatic lineage and produce mature blood cells. Other bone marrow cell types are also present, which, however, are undesirable in the areas of myocardial injury, such as osteoblasts, pericytes, and pre-adipocytes. In fact, in these mixed cell populations only a small proportion (approx. 1%) of bone marrow cells are progenitors or stem cells suitable for cardiac regeneration purposes (1). Among them, hematopoietic and mesenchymal stromal cells (MSCs), other mononuclear cells, CD34+ cells, CD133+ cells home in the bone marrow. However, unselected bone marrow cells did not substantiate breakthrough regenerative effect in clinical scenario.

Mesenchymal stromal cells (MSCs) are multipotent stem cells, and apart from bone marrow, they can be found in several organs indicating their importance in tissue regeneration in general. Pre-clinical studies reported their reparative capacity uniquely, regardless of their origin. MScs are immune privileged, less recognized by the host immune system and have immunosuppressive characters; for those reasons, they are preferred for allogeneic cell therapy. MSCs are known to secrete hundreds of proteins, such as growth factors (VEGF, HGF, IGF-1), anti-apoptotic and anti-inflammatory mediators, SFRP-2, angiogenin, cystatin, all of them are essential in cardiac regeneration (2, 3).

The broad use of unselected or selected bone marrow cells is limited by several factors, such as the extensive cell culture conditions and the several passages that are necessary to reach the required number of selected cells, as well as their usual autologous origin (sick cells from sick patients), or the narrow time window between harvesting and clinical application. In order to overcome the disadvantages of bone marrow derived MSCs, the use of adipose tissue-derived mesenchymal or stromal cells (ADSCs) were also explored in subsequent clinical trials. The usual source of the ADSCs is the abdominal adipose tissue, gained by liposuction. The ultimate advantage of ADSCs is the possibility to be produced under sterile GMP conditions, as ATMP (Advanced Therapy Medicinal Product), a “regenerative substance”, ready to use with long shelf life (commercial off-the-shelf product). Furthermore, ASCs grow faster than MSCs during culture expansion.

Other potential sources of cardiomyogenic cells that exhibit MSC properties have also been identified. Those includes endometrial regenerative cells, mesenchymal cells derived from menstrual blood, and those derived from endometrium. These cells typically express surface markers such as CD29 and CD105, suggesting MSC properties and they can exert cardiomyocyte-like action potentials.

The discovery of the cardiac stem cells (CSCs) and cardiosphere-derived cells (CDCs) (4) that are positive for self-renewing c-kit and clonogenic, opened up new directions in cardiac regenerative therapy and two phase I trials were initiated using those cells. The SCIPIO (5) and the CADUCEUS (6) trials were designed to investigate the effect of CSCs and CDCs in patients with subacute myocardial infarction and ischemic HF, resepectively. The SCIPIO trial demonstrated that intracoronary infusion of autologous CSCs led to better left ventricular ejection fraction in a small subset of patients (5) but CADUCEUS showed no effects on the primary endpoint (systolic function), although scar dynamics and the ability of the regenerative muscle to distend did improve (6).

Beside searching of new therapeutic cell types, further cell processing methods were developed to enhance the homing, vascularizing and muscle regenerative capacity of the injected cells. The Ixmyelocel-T composite is an expanded bone marrow mononuclear cell mixture, with about 200x higher number of M2 macrophages (anti-inflammatory cells) and 50x higher number of CD90+ BM-MSCs (regenerative cells). The Ixmyelocel-T Phase 2b randomized study was a part of the ixCELL-DCM trial, and included patients with ischemic dilated cardiomyopathy with an ejection fraction ≤35%. The percutaneous transendocardial delivery of Ixmyelocel-T led to significant reduction of clinical cardiac adverse events, without affecting the ejection fraction (7). The C-Cure cells were autologous bone-marrow origin

TABLE 1. Clinical cardiac cell-based regeneration studies including patients with heart failure

Study	Study acronym	Delivery mode	Rando-mized study	No of treated pts	No of controls	Type of cells	FUP duration	Treated pts EF baseline	Treated pts EF FUP	Comment
Erbs (12)		ic	yes	13	13	G-CSF mobilized circ. Progenitor cells	3 m	51.7±3.7	**58.9±3.2***	
Assmus (13)	TOPCARE-CHD	ic	yes	24 and 28	23	Circ. Progenitors or BM-MNCs	3 m	29±10 and 41±11	**39±10*** and 43±10	
Assmus (14)	TOPCARE-CHD Registry	ic	no	121	0	BM-MNCs	60 m	39.9±11.4	41.7±11.9	
Diederichsen (15)	DanCell-CHF	ic	no	32	0	BM-MNCs	12 m	33±9	34±10	
Bolli (5)	SCIPIO	ic	yes	16	7	c-kit pos.	4 m and 12 m	30.3±1.9 (SE)	**38.5±2.8 (SE)***	Phase I study
Makkar (6)	CADUCEUS	ic	yes	17	8	CDC	12 m	39±12	NA	
Smits (16		percut. Im	no	5	0	Myoblast	6	36±11	41±9	1st percu-taneous im study
Perin (17)		percut. Im	yes	14	7	BM-MNCs	4	20±9	**29±13***	
Perin (18)		percut. Im	yes	11	9	BM-MNCs	12	30±6	35.1±6.9	
Briguori (19)		percut. Im	no	10	0	BM-MNCs	12	53±10	57±16	
Fuchs (20)		percut. Im	no	27	0	BM-MNCs	12	48±9	50±7	
Beeres (21)		percut. Im	no	15	0	BM-MNCs	3 and 6	23±8	27±9	
Losordo (22)		percut. Im	yes	18	6	G-CSF-activated CD34+	6	NA	NA	
Beeres (23)		percut. Im	no	20	0	BM-MNCs	3 and 6	44±13	49±17	
Beeres (24)		percut. Im	no	30	0	BM-MNCs	12	51±12	54±12	
Tse (25)	PROTECT-CAD	percut. Im	yes	19	9	BM-MNCs	6	51.9±8.5	**55.6±8.8***	
Dib (26)	CAuSMIC	percut. Im	yes	12	11	Myoblast	12	NA	NA	
van Ramshorst (27)		percut. Im	yes	25	25	BM-MNCs	3	56	**59±11***	
Jiménez–Quevedo (28)		percut. Im	yes	12 DM	13 nonDM	BM-MNCs	NA	40/30	45/35	
Gyöngyösi (29)	MYSTAR	percut. Im	yes	30 early	30 late	BM-MNCs	12	38.4±5.8/ 37.7±6.0	41.9±8.0 /**41.3±9.0***	all pts in late group were cro-ss-over treated
Pokushalov (30)	ESCAPE	percut. Im	yes	55	54	BM-MNCs	12	27.8±3.4	32.3±4.1*	unusually high mortality in control group

Table 1 continued

Heldman (31)	TAC-HFT	percut. Im	yes	19 and 11	19 and 10	BM-MSC/placebo	12	35.7 / 28.1 / 35.9 / 36.2	NA	sign. Increase in viable myocardial mass in treated pts
Perin (32)	FOCUS-CCTRN	percut. Im	yes	61	31	BM-MNCs	6	34.7±8.8%	36.1%	diffreence between pts and co signif
Guijarro (33)	MESAMI pilot	percut. Im	no	10	0	MSCs	1 m and 12 m	29.4±2.0%	**35.7±2.5%***	LV ESV and 6-min walking test sign impr. In treated pts
Bartunek (8)	C-Cure	percut. Im	yes	21	15	Cardiopoietic SC	6 m	27.5±1.0%	**34.5 ± 1.1%***	
Bartunek (9)	CHART-1	percut. Im	yes	315	157	autol. BM-MNC + cardiogenic coctail	39 w	NA	NA	
Perin (34)	FOCUS-HF	percut. Im	no	20	10	Autol. BM-MNCs	6 m	41.5±11.2%	44±13.4%	improved QOL in treated pts
Mathiasen (35)	MSC-HF	percut. Im	yes	37	18	autol. BM-MSC	6 m	NA	NA	signif. Improved in treated pts
Perin (36)	PRECISE	percut. Im	yes	21	6	autol ADRC	6 m	NA	NA	WMSI improved in treated pts
Wojakowski (37)	REGENT-VSEL	percut. Im	yes	16	15	BM-CD133+	4 m	48.5±9.8%	46.8±11%	
Patel (7)	IxCELL-DCM-IHF	percut. Im	yes	66	60	ixmyelocel-T	12 m	NA	NA	sign. improved clinical outcome in treated pts
Henry (38)	ATHENA	percut. Im	yes	17	14	ADRC	6 m, 12 m	NA	NA	improved QOL in treated pts
Assmus (39)	REPEAT	ic	no	111	0	autologous BM-DC	24 m	NA	NA	comparator: single dose (n=186)
Assmus (49)	CELLWAVE	ic + shockwave (SW)	yes	82	21	autol. BM-MNC	4 m	37.2% (low-dose SW) and to 32.4 %* (high dose SW)	**to 39.9 %* (low-dose SW) to 35.5 %* (high dose SW)**	significant between BMCs+SW and placebo+SW
Kastrup (41)	CSCC-ASC FIM	percut. Im	no	10	0	allog. ASC	6 m	28.8%	31.7%	

* p<0.05 between treated and controls

Pts: patients, precut. Im.: percutaneous intramyocardial, ic: intracoronary, autol: autologous, allog: allogeneous, BM-MNC: bone marrow mononuclear cells, BM-DC: bone marrow-derived cells, ADRC: adipose tissue derived regenerative cells, SC: stem cells, MSC: mesenchymal stem cell, circ: circulating, m: month, NA data not available

Note: Studies are not presented if the number of patients in a stem cell treated group was less than 15 (except milestone studies), no left ventricular ejection fraction data were reported, solely treatment of subcutaneous injection of granulocyte-colony factor (G-CSF) was performed without intracoronary delivery of stem cells, or the stem cell injection was performed via surgical procedure. Publications containing subgroup analysis of previously reported studies were also excluded.

MSCs, subjected to a cardiogenic cocktail to trigger the expression and nuclear translocation of cardiac transcription factors in order to achieve lineage specification and maintaining clonal proliferation (8). After 3 passages, only cells with >2-fold induction of nuclear MEF2c were selected for the clinical administration (8). Cell therapy with the C-Cure cells led to a significant improvement in ejection fraction in a small cohort, while the larger randomized CHART-1 trial could not confirm those early results (9).

Application mode of cell therapy in HF patients

The various mode of applications, the advantages and disadvantages of the percutaneous intracoronary, intramyocardial and surgical direct intramyocardial delivery of cells or other regenerative substances have been previously summarized (10). Briefly, percutaneous intracoronary cell delivery represents the easiest way to transplant cells into the heart via the coronary arteries, allowing unlimited amounts of cells or injection volume, albeit with rapid wash-out and less efficient biodistribution, with consequently less homing of the cells. Percutaneous intramyocardial injection of cells leads to more exact spatial cell transplantation to the ischemic area, with less washout; however, the amount of the injectable cells is limited, and the procedure is more complicated and costly (11). Surgical direct intramyocadial injection allows direct delivery and the visualization of the cell transplantation into the heart, however, it requires open heart surgery and randomization and blinding in such clinical trials is difficult. Nevertheless, patients with ischemic HF have often multiple coronary lesions, previous myocardial infarction, or bypass surgery, or occluded vessels. For that reason, the direct intramyocardial delivery mode of therapeutic cells is presumably more appropriate as the intracoronary delivery method.

Clinical studies

Up to now, more than two hundred small or medium-large cell-based cardiac regeneration studies are registered in clinicaltrials.gov home page, involving patients with ischemic HF. Several of them have not even started yet, or prematurely stopped due to lack of sponsor or slow recruiting rate.

Table 1 lists the completed and published clinical cell-based therapy studies including patients with chronic ischemic HF (5–9, 12–41). Few studies with either intravenous or surgical intramyocardial delivery modes were not included, due to small number of such studies and patients. The *Table 1* shows the delivery mode, study design (randomized or not), the number of the treated and control patients, and the baseline and follow-up ejection fraction of the treated patients, in case these values were published.

Majority of the studies includes patients with low ejection fraction (<40%). Eight of the 35 listed studies (22.9%) includes 516 of 1962 patients (26.3%) used the intracoronary delivery mode, while the others used the percutaneous intramyocardial cell transplantation.

Four intracoronary cell trials (3 of them from the Frankfurt group) demonstrated significant improvement of the left ventricular function in patients with ischemic HF treated with cells. From the 10 randomized intramyocardial cell therapy studies, where baseline and follow-up LV EF were reported, 8 trials showed significantly better LV EF in the cell-therapy group as compared to the controls. However, the last 3 largest randomized trials (Ixmyelocel-T Phase 2b, CHART-1 and ATHENA) could not demonstrate significantly improved LV performance after cell therapy compared to controls, albeit significantly less clinical adverse event were observed in the Ixmyelocel-T trial and the quality of life was improved in the ATHENA study in patients receiving cell treatment (7, 9, 38).

Meta-analyses

To overcome the major obstacles of cardiac cell therapy trials, namely small size with slow patient recruitment in a relevant time frame, meta-analyses of the published data have been performed to reach the required statistical power. From the pooled data, the average EF increase with cell therapy has been found to be from –0.16% to 5.4% with variability across studies in population size, design, and method of EF evaluation (42, 43). In all, little to moderate therapeutic benefit from cell therapy has been reported in terms of survival or cardiovascular-related adverse events, but the largest meta-analyses were able to identify persistent improvement in other clinical endpoints and LV function (*Fisher* 2015) (43).

The major drawback of these meta-analyses is the high heterogeneity between included trials, and that they possibly exclude relevant studies reporting median values with non-normally distributed data. The gold standard type of meta-analysis is based on the individual patient data (IPD), the consistent use of unique definitions and the transparency of data sets, and can analyze subgroups for features that may be in association with cell therapy effectiveness.

The initial IPD meta-analysis was ACCRUE (Meta-Analysis of Cell-based CaRdiac studies), which published 12 randomized studies of intracoronary cell administration in patients with recent AMI showed no effect of cell therapy on LVEF or clinical outcomes, and found no predictors or patient characteristics associated with the benefit of intracoronary cell therapy (45, 46). The IPD meta-analysis of trials involving patients with ischemic HF is currently ongoing.

TABLE 2. Role of non-coding RNAs in cardiovascular diseases. Modified from Greco et al. (49)

Disease	Modulation	non-coding RNAs
Coronary artery disease	Upregulated	miR-135, miR-337-5p, miR-433, miR-485-3p
	Downregulated	miR-17, miR-92a, miR-126, miR-145, miR-147, miR-155
Unstable angina	Upregulated	miR-21, miR-25, miR-92a, miR-106b, miR-126, miR-134, miR-198, miR-370, miR-451, miR-590
Myocardial infarction	Upregulated	miR-1, miR-133, miR-208a, miR-208b, miR-328, miR-499, aHIF
	Downregulated	miR-27b, miR-126, ANRIL, LIPCAR
Heart failure	Upregulated	miR-29b, miR-122, miR-142-3p, miR-423-3p, miR-499,
	Downregulated	miR-29b, miR-107, miR-125b, miR-126, miR-139, miR-142-5p, miR-142-5p, miR-497

Further directions, secretomes, exosomes and non-coding RNAs

One of the major problems with the cardiac cell therapy is the low cell retention rate, and rapid distribution of the cells in remote organs (47). In contrast, almost all clinical studies suggested some benefit of the cell therapy, either in improvement of clinical symptoms, or reduction of adverse events or increase in LV function. The reason for the benefit of the cells in light of these findings may be attributed to the secretion of paracrine-signaling factors that exert promotional effects on the myocardium and vasculature.

According to the “paracrine hypothesis”, different stem cell types secrete tissue regenerative proteins and small molecules, like chemokines, cytokines, and growth factors. Several of these factors are recognized to improve cardiovascular function in acute or chronic cardiac tissue injury (48). The paracrine history paved the way to cell-free therapy approaches, e.g. cardiac regeneration without cell transplantation.

Furthermore, all cell types, also the injected stem cells secrete extracellular membrane vesicles such as exosomes and microparticles. Both of them are present naturally in all biological fluids, and store materials, including noncoding (nc)RNAs (miRNAs, lncRNAs), lipids and proteins. MicroRNAs are short, approximately 22 nucleotides long, and long noncoding RNAs are longer (>200 nucleotide), noncoding transripts that are post-transcriptional regulators of gene expressions and thus cell function. Dysfunction of ncRNAs has been associated with pathologies, including CAD and HF. Many of the ncRNAs are remarkably stable outside the cells, in the extracellular environment. The circulating non-coding RNAs are suggested to have paracrine mediator function in cardiac repair, involving several interacting cellular network and biological pathways to reduce cardiac inflammation, fibrosis and remodeling, and promote vascular growth and tissue regeneration, regulate survival of cells, and recruit and activate in situ stem and progenitor cell populations *(Table 2)* (48–50). Accordingly, a new era has evolved in the cardiac regeneration field, to replace the cells with various factors that regulate distinct pathogenic cell functions at molecular level.

In conclusion, cardiac cell therapy for patients with ischemic HF is still a promising option to reduce disease-related morbidity and mortality. In order to enhance the success of cardiac regeneration therapy, new molecular approaches using specific protein and ncRNA based factors are being assessed to achieve breakthrough in cardiac repair.

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