

Review Article

Stem Cell Therapy for Chronic Heart Failure

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Heat failure is an increasing clinical problem.¹ Its prevalence is estimated to be 1-2% in the Western world and its incidence approaches 1% per year.² As mortality from acute coronary syndromes, such as myocardial infarction, decreases due to revascularization therapy, more patients proceed towards the development of incurable chronic heart failure:³ incurable because of permanent loss of cardiac contractile tissue and a subsequent decrease of left ventricular performance. Unlike other organs such as the liver, the heart lacks an adequate auto-regeneration ability, although increased proliferative activity has recently been demonstrated after injury.⁴ Current treatment options, however, do not lead to more than moderate improvement in either the patient's quality of life or the prognosis.

Therapy for chronic heart failure

Medical

Pharmacotherapy is the first line of treatment for chronic heart failure. Practice guidelines emphasize the evidence-based use of angiotensin converting enzyme inhibitors (ACE-I), beta-blockers and aldosterone antagonists for improvement of prognosis as well as symptoms.⁵ Implementation of these guidelines, however, remains incomplete. For instance, ACE-I and beta-blockers are not uniformly prescribed, according to the European

Heart Survey.⁶ Next to lifestyle changes, submaximal exercise training is encouraged,⁶ but this approach is still currently being assessed.⁷

Surgical

The most effective approach for end-stage heart failure is replacement of the patient's heart by a donor heart. Perioperative complications and the need for life-long immunosuppression remain a limitation of the procedure. However, the 10-year survival rate of 50% on average represents a significant improvement over the natural course.⁸ In case of ineligibility for homologous transplantation, or when immunosuppression is contraindicated, there is an off-the-shelf solution in the form of continuous-flow blood pumps to support the damaged heart until transplantation becomes available.⁹ The total artificial heart provides for bridge-to-transplantation and improves pre-transplantation rates of survival, but cannot yet fully replace homologous transplantation.¹⁰

Experimental

Experimental approaches to improve heart function in chronic heart failure include adjuvant studies that increase and mobilize numbers of circulating peripheral progenitor cells by treatment with statins, erythropoietin, or granulocyte stimulating factor (G-CSF).¹¹⁻¹⁴ A very recent development

is gene therapy using adeno-associated viruses as vectors for sarcoplasmic-endoplasmic reticulum calcium ATPase 2a (SERCA2a) delivery; currently, two phase I clinical trials are in preparation.¹⁵

Limited self renewal of the heart

For decades the heart has been considered a post-mitotic organ with limited auto-regenerative capacity. It was generally accepted that the heart was composed of myocytes that are unable to divide. This classical view, however, has been challenged. Kajstura et al¹⁶ already demonstrated in 1998 myocyte replication in end-stage heart failure. In addition, Beltrami et al⁴ showed mitotic activity in human post-infarct border zone tissue. Furthermore, it has recently been shown that resident cardiac progenitor cell numbers in the failing heart were increased almost fourfold.¹⁷

The self-renewal capacity of the heart today, however, remains insufficient to prevent the development of heart failure. It has been hypothesized that attempts to enhance the intrinsic self-renewal process may form a promising approach.

Stem cell or progenitor cell therapy

Experimental studies have provided evidence that cell-therapy based treatment is promising and safe for the restoration of cardiac function or halting the progression of heart failure.¹⁸⁻²¹ The main objective was to replace dysfunctional, non-contractile fibrotic tissue with viable contractile cells, preferably electrically coupled, or to augment neovascularization.

The major part of clinical cell therapy for heart failure has focused on improving heart function after acute myocardial infarction.²²⁻²⁴ Stem cell therapy for acute myocardial infarction, as well as adjuvant therapy, are beyond the scope of this overview. The present paper is limited to stem cell therapy for chronic heart failure. To this purpose we performed a literature search starting in Pubmed, limited to human studies only. Based on search results we further explored available relevant studies in the English language. Both controlled and non-controlled studies for chronic heart failure were analyzed. Of the resulting studies 59% were non-controlled. Of these non-controlled studies about 65% indicated a positive effect on left ventricular function. One study reported that 80% of treated patients were no longer eligible for cardiac transplantation,²⁵ implying a beneficial effect of the therapy.

Positive effects on cardiac function have been reported in controlled studies as well. However, it must be taken into account that most of the positive results of controlled studies cannot be interpreted unambiguously because of many procedural variations in, for example, cell type, group size, inclusion criteria and investigational methods. Because most trials used a non-placebo control group, false positive results from subjective judgments, such as NYHA classification scores and quality of life questionnaires, cannot be excluded. Therefore, only functional parameters were analyzed. All controlled studies have been included in Table 1.

Effect

Most non placebo-controlled studies show an increase in left ventricular function, suggesting that the therapy is effective. For example, Perin et al²⁶ reported an increase of 3.65% in left ventricular ejection fraction in stem-cell treated patients compared with non-treated patients ($p=0.029$). In contrast, two out of three placebo-controlled studies did not confirm this significant increase. Hendrikx et al²⁷ showed that global left ventricular ejection fraction in their control group increased non-significantly from $39.5 \pm 5.5\%$ at baseline to $43.1 \pm 10.9\%$ at 4 months' follow up ($p=0.36$). The treatment group experienced an increase from $42.9 \pm 10.3\%$ at baseline to $48.9 \pm 9.5\%$ at follow up ($p=0.21$). Consequently, control and treatment group did not differ significantly at baseline ($p=0.19$), nor did results vary significantly at 4 months' follow-up ($p=0.41$). In addition, Menasché et al,²⁸ who compared 2 dosages of skeletal myoblasts with a placebo-controlled group, reported a median absolute change in left ventricular ejection fraction of 1.2% in the low dose group and 1.1% in the high dose group. These two studies suggest that there is no improvement in global left ventricular function after cell therapy. Interestingly, a placebo-controlled study by Tse et al²⁹ reported significant positive effects on cardiac function. Global left ventricular ejection fraction of controls did not change significantly from baseline to 6 months ($45.7 \pm 8.3\%$ vs. 45.3 ± 8.3) but in the treatment group an increase was observed (from $51.9 \pm 8.5\%$ to $55.6 \pm 8.8\%$, $p=0.044$). Tse's study was a non-surgical investigation, while the other two placebo-controlled studies were conducted in combination with coronary artery bypass grafting (CABG). This may suggest that the positive effect of CABG on left ventricular recovery may overshadow the effect of cell

Table 1. Overview of controlled studies of stem cell therapy for chronic heart failure in humans.

Cell type	Cells	Route of administration	Patients	Follow-up	LVEF/NYHA	Diagnosis	LV function			Ref.
							≤4 m	6 m	9-12 m >12 m	
Controlled trials										
BM-MNC	30·10 ⁶	Intramyocardial	21	2, 4 months	<40%	Chronic CAD	↑ vs. baseline			26
BM-MNC		Intramyocardial	23	2, 6, 12 months	<40%	End-stage ischemic cardiomyopathy	=	=	=	43
SkM	206·10 ⁶	Intramyocardial	42	4 years	≥20%-≤45% NYHA II-III	History of MI >90 days			=	30
BM-MNC	60-132·10 ⁶	Intracoronary	36	3 months		History of MI 5 months-8.5 years	↑			44
BM-MNC	3·10 ⁶	Intracoronary	28	7 days, 1, 3 months	<40%	History of MI	↑ vs. baseline			45
BM-MNC CPC	205·10 ⁶ 22·10 ⁶	Intracoronary	92	3 months		History of MI >3 months	↑			46
BM-CD133+, BM-CD133-/CD34+	CD133+: 17·10 ⁶ CD133-/CD34+: 8·10 ⁶	Intracoronary	24	4-28 Months	<40% NYHA I-II	History of MI >1 year	↑ vs. baseline	↑ vs. baseline	↑ vs. baseline	31
BM-CD34+	22·10 ⁶	Intramyocardial during CABG	20	1, 3, 6 months	≤35% NYHA III or IV	History of MI	↑	↑		34
BM-CD133+	6·10 ⁶	Intramyocardial during CABG	40	6 months		History of MI 2 weeks-3.2 years		↑		47
Placebo-controlled trials										
BM-MNC	Low: 17·10 ⁶ High: 42·10 ⁶	Intramyocardial	28	6 months	>30%	CAD		↑		29
BM-MNC	60·10 ⁶	Intramyocardial during CABG	20	4 months	<40%	History of MI	=			27
SkM	Low: 400·10 ⁶ High: 800·10 ⁶	Intramyocardial during CABG	97	6 months	≥15%-≤35% NYHA I-III	History of MI >4 weeks		=		28

AvG – average; BM – bone marrow; CAD – coronary artery disease; CPC – circulating blood progenitor cells; LV – left ventricular; LVEF – left ventricular ejection fraction; MI – myocardial infarction; MNC – mononuclear cells; NYHA – New York Heart Association; SkM – skeletal myoblasts; ↑ – significant increase in LV function; = – no change in LV function.

therapy in placebo-controlled studies. It is worth noting that in controlled trials regional function was very seldom measured.

Long-term effect

Only two controlled studies provided follow-up data over more than 12 months,^{30,31} of which one showed a positive sustained effect in the long term. In addition, a non-controlled long-term follow-up study by Hagège et al³² showed a sustained long-term positive effect. However, this last study also included surgical revascularization therapy. It is, therefore, not at all clear whether stem cell therapy results in sustained effects in the long term. Furthermore, relative small group sizes and the low number of controlled studies preclude conclusive evidence.

Safety

In general, two sources of autologous cells were used: bone-marrow derived cells and skeletal-muscle derived myoblasts. Overall adverse events related to cell therapy were generally not reported in these mainly short-term studies. However, extending the observations over a period of four years, Veltman et al³⁰ observed an 87% incidence of ventricular arrhythmias in patients who received skeletal myoblasts versus 13% in controls ($p=0.015$), casting doubt on the suitability of this cell source for therapeutic applications. Menasché et al²⁸ and Hagège et al³² also pointed out the proarrhythmic risk of myoblast implantation in their research, which they controlled by implantable cardioverter defibrillators and pharmacotherapy. Contrary to the aforementioned, Dib et al³³ did not report any increased risk of arrhythmias using skeletal myoblasts. Taken together, all studies reported that cell therapy for chronic heart failure is feasible and safe provided that precautionary measurements were taken in the skeletal myoblast studies. With respect to safety, it must be noted that because of the relative small group sizes, rare adverse events such as tumorigenesis could have easily been missed.

Cell type, number, functionality and route of administration

In order for cell therapy to be regarded as clinically relevant, many parameters remain to be optimized, including cell type, cell number, cell functionality and route of administration. From the controlled studies,

some interesting observations can be made. Hendriks et al²⁷ did not report an average significant improvement in left ventricular ejection fraction. Interestingly, they did show that patients who responded positively to the therapy in terms of a significant increase in wall thickening (5 of 9 stem cell treated patients) were treated with a significantly higher number of CD34+ cells. In addition, Patel et al³⁴ demonstrated a significant improvement using CD34+-enriched (>70%) fractions. Furthermore, two studies in which either CD133+ or CD133-/CD34+ fractions were used showed positive effects on cardiac function.^{31,35} Also in cell therapy for acute settings, Schächinger et al³⁶ suggested that positive results from their REPAIR-AMI trial, as opposed to the negative findings in the ASTAMI³⁷ trial, might be explained by a 3.5-fold higher number of transplanted CD34+ cells. In summary, all controlled studies in which mainly multipotent cells were transplanted show significant positive results, or at least a trend. Studies in which a more heterogeneous population, such as bone marrow mononuclear cells (BM-MNC), were used were less conclusive.

The cell numbers used in cell therapy for chronic heart failure differ considerably, as is clearly shown in Table 1. Numbers as low as $3 \cdot 10^6$ cells and as high as $800 \cdot 10^6$ were used. Clear correlations between the number of cells administered and the effect on left ventricular function were not observed. In one placebo-controlled study, however, significant decreases in left ventricular volumes in high-dose groups ($800 \cdot 10^6$ cells) versus low-dose groups ($400 \cdot 10^6$ cells) were observed.²⁸ On the other hand, Tse et al²⁹ used low numbers of cells ($17 \cdot 10^6$ - $42 \cdot 10^6$) and showed a significant effect on left ventricular function. Compared to the results shown in Table 1, clinical trials for acute infarctions that reported significant improvements used on average higher cell numbers (i.e. $245 \cdot 10^6$ and $2460 \cdot 10^6$).^{23,24} This indicates the importance of future dose-response studies.

Another factor that is associated with improvement is the functionality of the cells. Rouy et al³⁸ reported that the sickest patients in their trial showed the least benefit from cell transplantation. Assmus et al³⁹ concluded similarly. Dimmeler et al⁴⁰ reviewed the effect of age and disease and concluded that they impaired cell functionality. This fact may be regarded as a confounding factor for clinical studies.

Finally, the route of administration in the studies was not uniform. Cells were delivered either by intracoronary injection or directly into the myocardium, the latter frequently done during CABG. In all con-

trolled studies using the intracoronary route of administration, left ventricular function improved significantly. The same holds true for intracardiac cell injection during open heart surgery. This suggests that route of administration is not a decisive factor for successful delivery. However, direct comparisons between routes of administration in cell therapy for chronic heart failure have not been reported.

Conclusion

The clinical significance of cell therapy for chronic heart failure remains unproven. Results thus far are inconsistent. The effective cell type, cell number and route of administration still need to be determined. Group sizes in published studies are small and controls are often not present or studies are not placebo-controlled. Study inclusion criteria and investigational methods differ between studies, making outcomes hard to compare. This underscores the need for standardization in cell therapy trials. To guarantee reliable, clinically relevant results and to prevent placebo-related false positive effects, it is of utmost importance that studies are well designed, placebo-controlled, double-blind and randomized, as perfectly pointed out by Bienenfeld et al and exemplified by Leon et al.^{41,42} In other words, cell therapy for chronic heart failure remains a field that needs further investigation. It has, however, repeatedly been proven safe and, although the evidence is slight, most results indicate a potential for improving the heart function of patients with chronic heart failure.

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