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Potential Strategies for Clinical Translation of Repeated Cell Therapy

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Abstract

Despite encouraging preclinical findings, clinical trials of repeated cell therapy are relatively scarce. As a result, the potential of this treatment paradigm remains to be assessed. We propose that a carefully planned clinical trial design using repeated cell dosing could lead to significant progress in the field of cell therapy.

Keywords

Repeated Cell Therapy; Heart Failure; Ischemic Heart Disease; Dilated Cardiomyopathy

Although cell therapy has been used in clinical settings for almost two decades, the results of the clinical trials performed to date are not conclusive. Potential reasons for this inconclusiveness include different patient populations, stem/progenitor cell types, and delivery methods as well as insufficient sample sizes and suboptimal study design. Another important reason, however, could be the use of inadequate treatment protocols and, specifically, of a single dose of cells [1,2].

There is now a general consensus in the field that the majority of the cell-related effects result from paracrine mechanisms, and not from direct cell differentiation [3]. Furthermore, regardless of the delivery technique, the long-term engraftment of cells in the myocardium is low [3, 4], which limits the effects of paracrine mechanisms to the early period after cell transplantation. Because of the short-lived paracrine actions of a single cell administration, demonstrating a long-lasting clinical improvement may be difficult. In accordance with this hypothesis, the results of clinical trials in heart failure have shown an improvement of heart function early after cell therapy, with less favorable long-term results [5]. Additionally, within a given duration of follow-up, preclinical studies have shown that repeated doses have additive effects resulting in a significantly larger total effect [1, 6, 7]. Taken together, these considerations suggest that repeated cell administrations augment the efficacy of cell therapy

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DISCLOSURES

None.

not only by extending its *duration* in time but also by increasing its *magnitude* at a given time.

Repeated cell therapy has been investigated in a number of preclinical and clinical studies (Table 1). Despite differences in animal models, cell delivery techniques, and cell types used, the results of preclinical trials have been consistently positive, demonstrating a significant benefit of repeated cell doses [1,6–9]. In contrast, the results of the clinical trials of repeated cell therapy have been less consistent [10–15], which suggests a need for careful evaluation of the current findings in an attempt to improve the design of future clinical trials.

In the first randomized clinical trial of repeated cell therapy to date [15], our group enrolled 60 patients with nonischemic cardiomyopathy (NICM) and left ventricular ejection fraction (LVEF) <40% who were randomly allocated to repetitive cell therapy (group A, n=30) or single-cell therapy (group B, n=30). Patients received bone marrow stimulation, and 80 million $CD34^+$ cells were collected by apheresis and injected transendocardially. In group A cell therapy was repeated at 6 months. When comparing the groups at 1 year, we found no difference in the primary end-point, defined as change in LVEF (from 32.2% to 41.2% in group A and from 30.0% to 37.9% in group B, P=0.40). Similarly, we found no intergroup differences in NT-proBNP or exercise capacity.

The negative results of this study [15] may indicate lack of benefit from repeated treatment but may also reflect other factors, namely, differences in patient characteristics at the time of the first and second injections, timing of repeated cell injections, cell dose, number of injections, or pathophysiology of the underlying disease. To date, the majority of clinical trials of cell therapy in heart failure have enrolled patients with reduced LVEF, typically in the range between 30 and 45%. In these patients, LVEF<40% was associated with a significantly better response to cell therapy when compared with patients with higher LVEF [5]. In our trial of repeated cell therapy in NICM [15], the mean LVEF before the second cell injection was 39.1%, which was significantly higher than the LVEF at baseline (31.2%). When analyzing the effects of the second cell dose, we found a favorable response (improvement in LVEF of at least 5%) in 10 of 30 patients; in these 10 patients (“responders”), LVEF prior the second cell injection was significantly lower than in the 20 “non-responders” (34.9% vs. 40.0%, P=0.02), suggesting that there may be a “ceiling effect” for cell therapy and that patients with higher LVEF at the time of the second dose may have less benefit from this therapeutic approach. Therefore, when designing the protocols of future clinical trials of repeated cell therapy, one should consider using the same patient inclusion criteria for the first and second dose.

Although the paracrine effects of cell therapy are thought to be short-lived, clinical data on the time-course of the effects of cell therapy are limited. Current evidence suggests that the majority of the beneficial effects occur early after cell therapy, with no additional benefit accrued after the first year [5]. However, there is significant inter-patient variability in the response to the first cell dose. This suggests that instead of setting a fixed (and arbitrary) time interval for the repeated dose, one should consider choosing the time interval based on the individual patient response, with the goal of administering the repeated dose at the time when the effects of the first dose appear to cease. Therefore, after receiving the first dose,

more frequent monitoring of patients with serial echocardiograms may be warranted to identify the appropriate time for repeat treatment.

Contrary to the findings in preclinical trials, clinical studies have demonstrated that increasing the cell dose may not necessarily lead to incremental clinical benefits. In a preclinical rat model of ischemic heart failure, the investigators attempted to overcome this limitation by dividing the cell dose in three repeated injections [7]. The results of this study demonstrated that three repeated doses of cells were superior to one dose even though the total number of cells infused was the same. Therefore, it appears that repetitive dosing may offer a unique possibility to use higher cell numbers in clinical settings beyond the limitations of a single high-dose strategy. In addition, it seems self-evident that the benefits of repeated dosing may increase with the number of doses; accordingly, future clinical trials may consider administering more than two doses.

Of note, the majority of trials demonstrating beneficial effects of repeated cell dosing have been performed in patients with ischemic heart disease [10–14]. In contrast, the study of repeated cell dosing in NICM displayed a less favorable outcome [15]. Although the reasons for these differences are not clear, they may be related to the greater potential for myocardial recovery seen in patients with NICM. These findings suggest that the potential therapeutic benefit of repeated cell therapy may be particularly evident in patients with ischemic heart disease, and that future clinical trials should primarily focus on this subset of patients.

Although the studies reviewed above [10–15] have provided initial proof-of-principle, they were limited by the lack of a true control group because, except for the STEMI study [11], in all of the other trials the single-dose group did not receive a second (placebo) infusion, which may have affected left ventricular function and also would have allowed blinding. To date, no study has evaluated the effects of repeated cell therapy in patients with ischemic heart failure in a randomized, blinded, placebo-controlled fashion, and none has tested more than two doses of cells.

In conclusion, we believe that the potential utility of repeated cell therapy remains to be fully assessed and should be evaluated with careful, rigorous clinical trials. Based on the current preclinical and early clinical data, in appears that repeated cell dosing offers a unique opportunity to maximize the beneficial actions of cell therapy. However, in order to successfully translate the encouraging preclinical findings to the clinical arena, future clinical trials may consider stricter patient inclusion criteria both at baseline and at the time of repeated dosing (focusing on patients with lower LVEF and ischemic cardiomyopathy), the use of higher numbers of cells and more than two doses, a placebo-controlled design, and variable time intervals between repeated cell administrations.

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Table 1.

Pre-clinical and Clinical Studies of Repeated Cell Therapy

Study	Condition	No. of animals/ subjects with repeated injection	Cell type	Cumulative cell number (million)	Delivery	Time from the first to repeated injection	Follow-up	Primary end-point	Outcome
PRECLINICAL STUDIES									
Richardson (2014)[8]	Rat AMI model	12	MSC	2	IM	1 week	4 weeks	LVEF	Improved compared with single dose
Tokita (2016)[1]	Rat ischemic HF model	25	CPC	36	IV	35 and 70 days	3.5 months	LVEF	Improved compared with single dose
Reich (2016)[9]	Rat AMI model	48	CDC	2.2	IM	3 weeks	6 weeks	LVEF	Improved compared with baseline
Guo (2017)[6]	Mouse ischemic HF model	19	CMC	3	IV	2 and 4 weeks	2 months	LVEF	Improved compared with single dose
Tang (2018)[7]	Rat ischemic HF model	8	CPC	36	IV	35 and 70 days	3.5 months	LVEF	Improved compared with single dose
CLINICAL TRIALS									
Diederichsen (2008)[10]	Ischemic HF	32	BMMC	15	IC	4 months	12 months	LVEF	No difference compared with baseline
Yao (2009)[11]	AMI	15	BMMC	400	IC	3 months	12 months	LVEF	Improved compared with single dose
Gu (2011)[12]	Ischemic HF	15	PBSC/G-CSF	300–400	IC	6 months	12 months	LVEF	Improved compared with single dose
Mann (2015)[13]	Angina	23	BMMC	192	TE	4.6 years	12 months	Summed stress score	Improved compared with baseline
Assmus (2016)[14]	Ischemic HF	111	BMMC	274	IC	3–6 months	36 months	Mortality	Improved compared with predicted mortality

Study	Condition	No. of animals/ subjects with repeated injection	Cell type	Cumulative cell number (million)	Delivery	Time from the first to repeated injection	Follow-up	Primary end-point	Outcome
Vrtovec (2018)[15]	Nonischemic HF	30	CD34+	160	TE	6 months	12 months	LVEF	No difference compared with single dose

AMI, acute myocardial infarction; HF, heart failure; MSC, mesenchymal stromal cells; CPC, cardiac progenitor cells; CDC, cardiosphere-derived cells; CMC, cardiac mesenchymal cells; BMMC, bone-marrow mononuclear cells; PBSC, peripheral blood stem cells; G-CSF, granulocyte-colony stimulating factor; IM, intramyocardial; IV, intraventricular; IC, intracoronary; TE, transendocardial; LVEF, left ventricular ejection fraction