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**Moving forward on the pathway of cell-based therapies in ischemic heart disease and heart failure – time for new recommendations?**

Micheu MM. Cell-based therapies in IHD and HF – new recommendations

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**Abstract**

Although substantial advances have been made in treating ischemic heart disease and subsequent heart failure, the overall morbidity and mortality from these conditions remain high. Stem cell-based therapy has emerged as a promising approach for prompting cardiac rejuvenation. Various cell types have been tested in the clinical arena, proving consistent safety results. As for efficiency outcomes, contradictory findings have been reported, partly due to inconsistency in study protocols but also due to poor survival, engraftment and differentiation of transplanted cells in the hostile milieu of the ischemic host tissue. Studies have varied in terms of route of delivery, type and dose of implanted stem cells, patient selection and randomization, and assessment of therapeutic effect. Founded on the main achievements and challenges within almost 20 years of research, a number of official documents have been published by leading experts in the field. Core recommendations have focused on developing and optimizing effective strategies to enrich cell retention and their regenerative potential. Issued consensus and position papers have stemmed from an unmet need to provide a harmonized framework for future research, resulting in improved therapeutic application of cell-based therapies for cardiac regeneration and repair.

**Key words:** Stem cell therapy; Ischemic heart disease; Heart failure; Cardiac regeneration; Recommendations

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**Core tip:** Ischemic heart disease and resulting heart failure remain a major public health problem worldwide in spite of therapeutic progresses. Almost two decades ago, stem cell-based therapy appeared as a promising method to stimulate cardiac regeneration. Based on the main findings and challenges faced during clinical trials within this timeframe, a number of consensus and position papers have been issued by key opinion leaders, with the specific aim to empower cell-based cardiac repair and regeneration in patients with the aforesaid maladies.

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**INTRODUCTION**

In spite of standard-of-care therapies, ischemic heart disease (IHD) remains one of the leading causes of early death and disease burden worldwide, leading to almost 9 million deaths and 170 million disability-adjusted life years globally in 2017[1]. The poor prognosis is related to the reduced endogenous regenerative ability of the adult human heart. Evidence-based disease management greatly improves patient outcomes, but it does not completely prevent myocyte injury and consequent adverse cardiac remodeling. Ongoing efforts are being made to develop alternative strategies to prompt the restoration of both cardiac structure and function. Advances in understanding stem cell (SC) biology have led to the development of stem cell-based therapy (SCT), which holds high therapeutic promise. The rationale behind SCT is that the supplied cells will facilitate the generation of functional cardiomyocytes and new blood vessels, either by exogenous regenerative responses or by activating endogenous renewal mechanisms[2].

**THE PAST**

Since the first in-man SCT for IHD[3], a substantial number of clinical trials (CTs) have been finalized and comprehensive reviews and meta-analyzes have been published, yielding inconsistent results[4,5]. But when it comes to papers expressing opinion and recommendations from expert authorities, their number is not so impressive. Since current guidelines on SCT in IHD and heart failure (HF) are lacking, experts in the field provided harmonized statements in order to move forward the clinical application of cell-based therapies for cardiac regeneration and repair; three position papers and two consensus documents have been put out in the last 13 years (Figure 1).

The first document of its kind was presented in 2006, when the Task Force of the European Society of Cardiology (ESC) published a consensus document on the use of autologous cell therapy for repair of the heart[6]. Although the 2006 paper is rather obsolete given the existence of an updated version[7], it has the merit of establishing a framework for upcoming research.

It took a decade until new papers were issued, a timespan in which important data have been offered by completed CTs. Provided recommendations have been formulated to address the main limitations raised within prior hallmark studies, such as reduced survival and engraftment of delivered cells in ischemic myocardium, lack of effective differentiation of adult SCs into mature and functional cardiomyocytes, insufficient activation of resident cardiac SCs, inadequate electrophysiological integration of the implanted cells with native myocardium, and the use of inappropriate end-points for assessing the outcomes of SCT. Hence, continual development of carrier materials and priming strategies (such as genetic and pharmacological modification) to improve SC retention, survival and differentiation has been recommended. A particularly important aspect is related to the type of SC to be transplanted, which should be carefully chosen. Due to adverse events, the skeletal myoblast is no longer of interest. First-generation cells, such as bone marrow - derived mononuclear cells (commonly referred to as BM-MNCs) or mesenchymal stem cells (MSCs), are considered to prompt endogenous repair mechanisms, while second-generation cells, such as pluripotent SCs and cardiac stem cells/cardiac progenitor cells (CSCs/CPCs), are believed to hold exogenous regenerative potential and actually replace the injured myocardium. Therefore, diverse cell types or a mixture of cell types have been suggested to be tested in randomized CTs. Nevertheless, possible confounders such as gender, age, comorbidities, and daily medications, should permanently be taken into account. Last but not least, the necessity of employing “hard clinically meaningful endpoints” to determine the actual impact on disease burden has been emphasized[2,7,8].

Notably, disease-specific recommendations have been also envisaged[7]. On the subject of launching additional autologous bone marrow cell CTs in acute myocardial infarction settings, the consensus was to await results from the BAMI trial[9]. BAMI was designed as the largest phase Ⅲ randomized CT with the precise goal to provide a conclusive answer whether BM-MNCs plus standard of care therapy can lead to a 25% reduction in mortality when compared to best medical care alone[10]. It is to emphasize that the study protocol was substantially revised, as the accrual rate was significantly impaired (375 randomized patients instead of the initial target of 3000 patients). Still, the results are eagerly awaited, and the study is being reconsidered as an estimation trial with the aim to assess the treatment effect and event rates in the SCT group. Until now, successful standardization of the bone marrow procurement and cell manufacturing technique has been reported. The full findings will be released after October 2019 (the estimated study completion date). In regard to SCT in chronic HF, the recommendation to use cardiopoietic cells - either primary or engineered - is reiterated. In view of the recognized safety of SCT, repeated administration should be planned in order to achieve improved long-term clinical outcome[7].

Of note, some of the aforementioned recommendations have already been translated into practice. For example, Bartunek and colleagues used a combination of cardiogenic growth factors to direct patient-derived MSCs toward a cardiopoietic phenotype[11,12]. Lineage specified MSCs proved to exert beneficial effects on cardiac remodeling, exercise capacity and quality of life[13,14].

Furthermore, a four-arm randomized CT has been designed with the aim to compare the restorative capacity of autologous bone marrow-derived MSCs and c-kit+ CPCs, either alone or in combination, in patients with ischemic HF. The estimated study completion date is May 2020[15].

While the aforesaid studies employed adult SCs, there was a single CT that used human embryonic SC-derived CD15+ Isl-1+ progenitors to treat patients with severe ischemic HF (the ESCORT study)[16]. Regardless of study limitations (*i.e.* small sample size, lack of blinded assessment, confounding effect of the concomitant coronary artery bypass grafting), the trial provided proof of concept for further robust studies.

**THE PRESENT**

In light of today’s knowledge, the very recent document published on behalf of ESC has focused on strategies to boost cell delivery and retention within native area by combined administration of cells, biologically active molecules and bio-materials (*e.g*., hydrogels, cell sheets, prefabricated matrices, microspheres, and injectable matrices)[17]. Cutting-edge tissue engineering (TE) approaches have been shown to increase the long-term cell retention of more than 80%, and for that reason they have emerged as valuable tools to advance cell therapies for IHD and HF. The use of materials that do not trigger inflammatory or foreign body responses (such as naturally derived polymers with an anti-inflammatory activity, extracellular matrix components, and materials with controlled release of anti-inflammatory/immunosuppressive molecules) is favored.

Also, the therapeutic potential held by human induced pluripotent stem cells (hiPSCs) is emphasized. Preclinical research revealed that transplanted hiPSC-derived cardiomyocytes (hiPSC-CMs) were able to persist, mature and proliferate within the host myocardium, causing improved cardiac function in recipient animals[18-20]. For an enhanced regenerative outcome, combinations of cells and bio-materials have been employed. For example, in a porcine ischemic cardiomyopathy model, transplantation of hiPSC-CMs cell sheets together with an omentum flap as a source of blood supply yielded better results compared with hiPSC-CM administration alone[21]. Similarly, co-transplantation of multiple hiPSC-derived cardiovascular cell types (*i.e.* cardiomyocytes, endothelial cells and smooth muscle cells) with a 3D fibrin patch impregnated with a pro-survival factor resulted in reduced cardiomyocyte apoptosis, diminished infarct size, and improved cardiac function[22]. However, the use of iPSC-CMs is not without risks (*i.e*. graft-related arrhythmias). For a safe and effective iPSC-based therapy, targeted cardiomyocyte subtype specification and functional maturation are of the essence. Accordingly, sustained efforts have been made to attain specialized, mature hiPSC-CM phenotypes, which could be further used for human engineered heart muscle constructs[23-25].

Another topic evoked by the authors of the ESC position paper refers to prompting cardiac regeneration by cell-free *in situ* strategies, such as injection of materials containing instructive signals for cardiac cell reprogramming or SC-derived secretome survival factors. In particular, direct cellular reprogramming of cardiac fibroblasts seems most appealing, given their abundance in infarcted myocardium. Indeed, prior studies have demonstrated that fibroblasts can be driven directly into cardiomyocytes by distinct combinations of lineage-significant transcription factors or microRNAs[26-30]. Of note, induced *in situ* fibroblast reprogramming improved cardiac function in animal myocardial infarction models, with 30%-40% increase in left ventricle ejection fraction and reduction of fibrotic scar by up to 50%[31].

At present, with very few exceptions (Table 1[16,32-34]), the use of tissue-engineered constructs for myocardial regeneration is still in the preclinical phase. To expedite TE and cell-based therapies for cardiac repair, the experts from the ESC Working Group on Cellular Biology of the Heart have issued several key statements. Hence, more effective TE strategies to increase cell retention should be further developed and optimized (including 3D printing to augment the biological ability of TE products). Of note, the whole fabrication of products should be conducted in agreement with regulatory demands, comprising proof of concept in rodent and large animal models[17].

**THE FUTURE**

With BAMI’s results being expected to be released and pluripotent SC-cardiac derivatives entering the clinical arena, it seems like these are exciting times for mending broken hearts. Hence, one can only ask oneself: what next?

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Grade E (Poor): 0



**Figure 1 Timeline of expert opinions in cell-based therapies for cardiac regeneration and repair.** ESC: European Society of Cardiology; TACTICS: Transnational AllianCe for regenerative Therapies In Cardiovascular Syndromes.

**Table 1 Ongoing/completed human clinical trials for cardiac tissue engineering**

|  |  |  |  |
| --- | --- | --- | --- |
| **Clinical trial name** | **Trial identifier** | **Target sample size** | **Status** |
| Epicardial Infarct Repair Using CorMatrix®-ECM: Clinical Feasibility Study (EIR) | ClinicalTrials.gov Identifier: NCT02887768[32]  | 8 | Completed |
| Transplantation of Human Embryonic Stem Cell-derived Progenitors in Severe Heart Failure (ESCORT) | ClinicalTrials.gov Identifier: NCT02057900[16]  | 10 | Completed |
| Myocardial Assistance by Grafting a New Bioartificial Upgraded Myocardium (MAGNUM Trial) | -  | 20 | Completed  |
| A Study of VentriGel in Post-MI Patients | ClinicalTrials.gov Identifier: NCT02305602[33]  | 15 | Active, not recruiting |
| Clinical trial of human (allogeneic) induced pluripotent stem cell-derived cardiomyocyte sheet for severe cardiomyopathy | UMIN-CTR Clinical Trial ID: UMIN000032989[34] | 3 | Not yet recruiting |