Editorial

Mesenchymal stromal cell therapy as treatment for ischemic heart failure: the MSC-HF study

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Ischemic heart disease (IHD) is becoming a major health problem worldwide. Advanced revascularization procedures and medical interventions have significantly reduced the number of deaths due to IHD in the past decades. However, they have left an increasing number of patients who suffer from ischemic heart failure (HF) and often have no further treatment options (1). Approximately 20% of patients diagnosed with HF die in the following 12 months and up to 50% of them die within 5 years of diagnosis (2). The incidence of repeated hospitalizations and reduced quality of life of such patients is posing, and will continue to pose, a considerable economic burden for healthcare providers across the globe. Consequently, there is an unmet clinical need to develop novel treatments to reduce mortality and improve quality of life of patients with IHD and HF. Regenerative cell therapy approaches have been at the forefront of clinical investigations in cardiology for the last 15 years.

Bone marrow- and blood-derived cells have been used in most clinical trials. Bone marrow and blood mononuclear cells (MNC), hematopoietic progenitor cells (HPC) or mesenchymal stromal cells (MSC) have been administered to patients who have suffered a recent myocardial infarction (MI) as well as those with symptomatic ischemic HF (3). However, it is still unclear whether cell-based therapies represent an effective treatment for these patients (3-7). There is also a need to define the optimal cell therapy approach: the best cell type to be used in the clinic, the best delivery system and the patient group who would benefit most from these treatments. Currently, the number of patients included in regenerative cell therapy studies may not be sufficient to find the correct answers to these still unresolved questions.

Bone marrow-derived MSC are known to provide supporting cells (e.g., stroma) for hematopoiesis and angiogenesis (8,9) and to exhibit a strong immunosuppressive activity (10). MSC-like cells have also been isolated from umbilical cord, amniotic fluid and adipose and cardiac tissues (8,11). Their presence in those tissues and their adaptability to be cultured in large quantities highlight their relevance and thus their potential use in tissue repair. Administration of autologous bone marrow MSC as treatment for severe ischemic HF has yielded positive results in Phase I clinical trials (12,13). Although promising, these results required confirmation in larger double-blinded randomized clinical studies.

The MSC-HF study (bone marrow-derived mesenchymal stromal cell treatment in patients with severe HF) was the first randomized, double-blinded, placebo-controlled trial designed to address the intra-myocardial delivery of autologous bone marrow-derived MSC in patients with severe ischemic HF and no further treatment options. The primary end-point of the MSC-HF study was to detect change in left ventricular end systolic volume

(LVESV), measured by magnetic resonance imaging (MRI) or computed tomography at 6 months follow-up. The secondary end-points included changes in left ventricular ejection fraction (LVEF), stroke volume, cardiac output, myocardial mass and scar size, as well as HF and angina functional class and quality of life (14).

In a previous non-randomized study, the same team established for the first time the intra-myocardial injection of bone marrow-derived MSC, treating 31 patients with chronic IHD (15). The rationale behind the MSC-HF trial (16) was based on the results of the preceding trial (15) and randomized phase I trials (12,13) which demonstrated the safety of the treatment and showed improved heart function and quality of life in patients with HF. The MSC-HF trial, which estimated a change in LVESV of 10 mL with an assumed standard deviation (SD) of 11.1 mL and a statistical power of 90% (16), recruited 60 participants. Participants enrolled in the study were diagnosed with HF, were New York Heart Association (NYHA) class II–III, had LVEF <45% and no further treatment options. They were randomized (2:1) to receive either bone marrow-derived MSC [40] or placebo [20]. Fifty five patients completed the 6 months follow-up (37 MSC-treated and 18 placebo controls). The MSC-HF study achieved its primary end-point, cell-treated patients showed a significant reduction of LVESV compared to patients who received placebo (14). Additionally, there was a significant improvement in LVEF, stroke volume and myocardial mass measured by MRI. No differences in severe adverse effects (SAEs), such as number of deaths and hospitalizations, associated to the treatment were observed. Although promising, the results are based on small number of events, and therefore, any further conclusion should be considered with caution. N-terminal pro B-type natriuretic peptide (NP-proBNP), a marker used to evaluate the severity of HF, was unchanged when comparing levels at baseline and end of study or between treatment groups. Furthermore, no differences in favor of cell treatment were observed in infarct scar size, NYHA class, exercise capacity or quality of life. Whilst functional classification, exercise capacity and quality of life are more subjective surrogates, the expectation was that MSC would reduce the infarct scar size as previously reported (13). A trend towards scar size reduction was observed, but only 17 patients (out of 60) underwent MRI, suggesting that with larger number of patients previous results may have been confirmed.

As mentioned above, there is a need to define the best cell therapy approach. The MSC-HF trial is an important study that paves the way into the design of future clinical trials in the field of cardiac regenerative cell therapy. Patients diagnosed with chronic ischemic HF, with no further treatment options, should be the primary target patient population for cardiac regenerative cell therapies because of their reduced quality of life and the poor prognosis of the disease. A recent review of randomized trials has indicated that there is robust evidence to suggest that cell-based therapies may have a beneficial effect complementing standard treatments when administered to patients with HF, but the evidence is unclear in patients who have suffered a recent MI (7). In the aforementioned patient target population, with stable chronic ischemic HF, the time interval between diagnosis and delivery of the treatment is not limiting. Intra-myocardial cell injection using state-of-the-art catheter injection systems (e.g., NOGA™ system) allows mapping and precise delivery of cells into viable and hibernating heart muscle. The injected cells are unlikely to engraft in the ischemic myocardium but they may persist long enough to exert their beneficial therapeutic effect. Intra-myocardial cell injection seems to be more efficient than intra-coronary administration (17). This is most likely due to the higher level of cell retention at the delivery site. In chronic phases of the disease the timing between the isolation of the cells and their delivery to the patients is less restrictive than in the acute phase. Autologous bone marrow and blood MNC were the ideal candidate cells to be tested following acute MI; the cells can be isolated and administered to patients straightaway. In the chronic phases of the disease there is a chance to evaluate different cell products that require preparation or modification. MSC and MSC-like cell populations can be isolated from most tissues of the body and cultured in large quantities for clinical applications (11). Because of their immunomodulatory properties, they can be used in allogeneic transplantation settings (12), or as an 'off-the-shelf' product. The manufactured end-product can be quality controlled and fully characterized before it is transplanted back into patients. Still the question remains; how do these cells work? For MNC this question remains unanswered, primarily because MNC are a mixture of cells with different functions (e.g., monocytes, macrophages, lymphocytes, dendritic cells, etc.). Bone marrow MSC are known to support hematopoiesis and angiogenesis (8,9). Their supportive function suggests that they would exert their beneficial effect by paracrine mechanisms (18). However, it is not that simple. The term paracrine is almost synonym of 'bag of goodies', admitting that there is still

a lot to learn about how the MSC secretome could have an immunomodulatory, anti-apoptotic, pro-angiogenic, growth-promoting, anti-fibrotic and chemoattractant effect (19), whether all these effects are really beneficial to the ischemic myocardium and whether a cell-free product could be sufficient (bystander effect) or cell-cell interaction will be necessary. Are we ready for MSC and MSC-like to take the baton in the cell therapy relay?

In summary, the MSC-HF is the largest randomized placebo controlled double-blinded trial of autologous bone marrow-derived MSC administered to patients with stable ischemic HF to date. The primary outcome measured in this trial, LVESV, is a strong independent predictor of mortality in ischemic HF (20). Therefore, and although the MSC-HF study is underpowered to detect differences in the risk of mortality and the follow-up was relatively short, its results would suggest that a reduction of LVESV in favor of MSC treatment could forecast a reduction in the risk of mortality. Only an adequately powered, randomized placebo controlled phase III trial could confirm this.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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