Clinical trials in cardiovascular cell therapy: where we are going

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In the last two decades, cell-based therapies have emerged as a potential promising chance for patients with acute myocardial infarction (AMI), chronic ischemic heart failure (CIHF) and critical limb ischemia (CLI). Different cell types have been proposed as therapeutic candidates for myocardial and vascular regeneration, including mononuclear cells and mesenchymal stem cells derived from bone marrow (BM), peripheral blood or adipose-tissue. More recently, a population of resident cardiac stem cells directly obtained from cardiac tissues has been described in literature.

Major approaches considered in AMI clinical trials are the indirectly mobilization of endogenous BM cells with cytokines and the directly intracoronary infusion of adult BM cells. A recent meta-analysis, which comprised a pool of 12 studies focusing specifically with the intracoronary cell delivery in patients with recent AMI, reported no effect on clinical events or changes in left ventricular function (LVF) and remodeling. However, in a similar cohort of patients, authors found that autologous BM cells infusion is associated with a moderate but statistically significant improvement of LV systolic function and remodeling in patients after STEMI. Regarding the endogenous mobilization approach, a number of previous meta-analysis have summarized the role of granulocytes-colony stimulating factor (G-CSF) treatment in this clinical setting. All these reviews have documented G-CSF to be safe although diverging results of clinical efficacy state.

In the context of CIHF, surgical and interventional trials have been conducted to investigate stem cells effects in sub-acute and chronic ischemic cardiomyopathy. Surgical studies are commonly designed to combine epicardially stem cell injection with coronary artery bypass grafting. Available systematic review and meta-analysis of randomized controlled trials (RCTs) showed that cardiac dysfunction and remodeling improved significantly with intramyocardial delivery of BM cells. Interventional studies include intracoronary standard balloon and trans-endocardial catheters specifically designed to infuse biological agents. While the first delivery method has proven a long-term beneficial effect in favor of cell therapy reducing the number of deaths and the risk of re-hospitalization, meta-analysis focusing on trans-endocardial injection are not yet available. However, many clinical studies have been published so far with largely positive indications of efficacy in terms of cardiac function and myocardial perfusion improvements.

Cell therapy has recently gained interest as a potential treatment option even for refractory CLI, with the goal to increase blood circulation in the ischemic limb. Different cell lineages have been delivered to affected limbs both *via* the intramuscular or intra-arterial route. A recent meta-analysis analyzed a total of 12 RCTs. When major amputation and amputation-free survival were considered as the primary end-points, beneficial effects of BM cells therapy were observed for both subjective and surrogate objective end-points. However, when the analysis was limited to the 7 placebo-controlled RCTs, the beneficial effect on major amputation rates and amputation-free survival was reduced and not significant, indicating that a placebo in the control arms is necessary. Well-designed larger placebo-controlled trials are required to establish the efficacies of these novel therapies. Furthermore, the long-term effects of these therapies should be verified.

In summary, while these studies have been proven safe and feasible without notable side effects, mixed outcomes in terms of clinical benefits have been reported. Looking at ongoing clinical trials and large phase III trials, it is conceivable that in few years new knowledge will be available creating the opportunity for cardiovascular cell therapy to be a routine procedure in clinical scenarios.