Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Editorial | Published 25 July 2012, doi:10.4414/smw.2012.13633
Cite this as: Swiss Med Wkly. 2012;142:w13633

STIM-ulation for the big trial

Christian A. Arranto

Departments of Anaesthesia and Medicine, and Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, USA

Ischaemic heart disease is one of the leading causes of morbidity and mortality in the industrialised world. Although pharmacological and interventional strategies for revascularisation have improved the outcome of ischaemic heart disease, the possibility of reversing progressive ventricular remodeling remains a major unresolved clinical problem. Furthermore, after myocardial infarction the endogenous regenerative capacity of the damaged organ is not sufficient to restore ventricular mass and function. Ventricular dilation and relative wall thinning enhance the mechanical load on the surviving cardiomyocytes, triggering a cascade of events that lead to severe myocardial dysfunction and, ultimately, terminal failure. Novel therapeutic approaches are therefore needed, pointing to exogenous and endogenous stem/progenitor cells as a potential form of treatment for this devastating disease [1–7].

Studies in animals have suggested that adult bone marrow stem cells transdifferentiate, possessing the unique capacity to create cardiomyocytes and coronary vessels, critical for the regeneration of the infarcted myocardium. These experimental findings have prompted numerous clinical trials, which collectively have shown relatively positive results. However, rapid implementation of bone marrow mononuclear cells (BM-MNC) in patients affected by acute myocardial infarction has stimulated heated discussion in the scientific community, with strong supporters and equally charged opponents of this type of cell therapy for the human disease. Numerous questions had to be addressed in clinical trials: method of administration, timing of delivery, cell type, number of cells and, most importantly, the safety and feasibility of this approach.

Many protocols for stem cell treatment have been used, including intravenous, transarterial, intracoronary and intramyocardial (including transepicardial and transendocardial) administration modalities. The least invasive route of delivery is intravenous infusion, which has the disadvantage that the majority of cells may be trapped in the pulmonary circulation [8]. Currently, the most frequently adopted method in stem cell therapy is injection of bone marrow progenitors via an over-the-wire balloon in the coronary artery supplying the ischaemic area. Although inflation of the balloon causes a transient ischaemic period, this intervention is essential to promote translocation of the infused cells through the vessel wall, their homing to the injured myocardium, and initiation of the repair process.

In previous clinical studies intracoronary and intramyocardial routes of administration resulted in similar improvements to left ventricular function. In both cases a low number of radiolabelled BM-MNC were retained in the tissue [9, 10], but a beneficial effect was recorded haemodynamically and in terms of quality of life.

The paper by Moccetti and collaborators in this issue of the journal reports the results of a 5-year follow-up of the STIM study [11]. BM-MNC were delivered within 3 days after the acute event, a variable that appears to be relevant for the efficacy of this form of cell therapy. In the REPAIR-AMI trial [2], the most favourable effect on LV function was observed when cells were given 5–7 days post-myocardial infarction (MI). Moreover, the LateTIME trial showed no improvement of LV function if BM-MNC were injected 2–3 weeks after MI [12]. The results of a randomised trial comparing early versus late injection of BM-MNC are expected from the SWISS-AMI trial (clinicaltrial.gov, number NCT00355186) later this year.

In the STIM study the sustained increase of left ventricular ejection fraction (LVEF) by 8 absolute points in echocardiography in the bone marrow-treated group is similar to the long term results of the TOPCARE-AMI trial [13]. In contrast, the BOOST trial showed that the early (6-month) improvement of LVEF in the treatment group was not present 5 years later [14].

The BM-MNC fraction obtained after density gradient centrifugation is composed of a heterogeneous mixture of cells including haematopoietic stem cells, endothelial progenitors and side population cells. The heterogeneity of BM-MNC may be one of the factors responsible for the conflicting results of apparently similar trials. Experimental data support this possibility: CD34+ cells collected from healthy volunteers and injected into the acutely infarcted rat heart showed superior therapeutic efficacy with respect to unselected circulating mononuclear cells [3]. Interestingly, improvement of LVEF in the FOCUS-CCTRN trial was associated with higher bone marrow CD34+ and CD133+ cell counts [15].

The mechanism by which the infused bone marrow-derived cells act is poorly understood. Whether BM-MNC acquire the cardiomyocyte, smooth-muscle cell and endothelial cell

lineages reconstituting the lost myocardial tissue is uncertain; c-kit-positive haematopoietic stem cells generate parenchymal cells and coronary vessels integrated structurally and functionally within the recipient myocardium [4]. Additionally, BM-MNC may exert a paracrine effect activating resident cardiac stem cells and promoting the endogenous repair process. These modalities of action are not mutually exclusive and the therapeutic effect of bone marrow-derived cells is most probably mediated by multiple mechanisms.

A recently published meta-analysis showed that overall mortality in cell-based therapy is low. Mortality was not significantly different in short- and long-term follow-up. The incidence of reinfarction, arrhythmias, restenosis or hospital readmission was similar between BM-MNC treated patients and patients in the control arm [16].

The mixed results of clinical trials to date underline the relevance of studies such as the STIM, which, although small and non-randomised, will contribute to a better understanding of the effects of cell-based therapy in patients with ischaemic heart disease. Future large phase III clinical trials such as the BAMI trial (clinicaltrial.gov, number NCT01569178) may show whether a single injection of autologous BM-MNC is safe and reduces all-cause mortality in patients after myocardial infarction. In conclusion, Moccetti and colleagues' study exemplifies the fact that cell-based therapy in acute myocardial infarction is beneficial and safe in the long term, which must be the ultimate goal for all of us.

Funding / potential competing interests: No financial support and no other potential conflict of interest relevant to this article was reported.

Correspondence: *Christian Arranto, MD, Brigham and Women's Hospital, Harvard Medical School, 75 Francis St, Thorn 1305, US-Boston, MA 02115, USA,* *carranto[at]partners.org*

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