INTRODUCTION

The two adult types of bone marrow (BM) can be distinguished: the red marrow consisting of hematopoietic tissue, including Hematopoietic Stem Cells (HSCs) capable of producing around 500 billion blood cells per day; and the yellow marrow mainly made up of fat cells. BM contains two types of stem cells: hematopoietic (which can produce blood cells) and stromal (which can produce fat, cartilage and bone).

Mesenchymal Stem Cells (MSCs), first described in 1970 in BM, emerged as an extremely promising therapeutic cell based agent for tissue regeneration and were broadly characterized in that sense. In vitro studies demonstrated that MSCs present attractive characteristics like immune-regulatory effects; capacity to stimulate neovascularization, endogenous stem cell proliferation and differentiation, capacity to modify the micro-environment, prevent scarification, fibrosis and aptitude to differentiate into various mesoderm derived tissue. Notably, myocytes and cardiomyocyte differentiation ability was shown in multiple studies. All together these properties drove enthusiasm for MSCs and particularly BM derived MSCs (BM-MSCs) use in cardiac regeneration. MSCs represent 0.001 to 0.01% of BM nucleated cells and, it is now broadly accepted that MSCs cultures represent a mix of various cells with various degrees of "stemness".

The unforeseen discovery that HSCs isolated from BM present the ability to repair infarcted myocardium also prompted extensive research in this direction. Though, HSCs only represent ~0.01% of BM mononucleated cells, and there expansion in vitro remains elusive, therefore, clinical trials to date relied on whole BM use, impairing the clear identification of which cellular actor drives the observe effect.

Therefore, very short time after the publication of the first experimental study of the use of Bone Marrow Cells (BMCs) for the treatment of post Myocardial Infarction (MI) heart failure (HF) in a small animal model, clinical trials of this form of therapy started. This was followed by an extremely large number of trials with mixed results, and even the alarming establishment of commercial clinics in different countries.

All together, these findings lead in the last year to witness the publication of several trials in the field using either whole BMCs or BM-MSCs. The results of the most recently publish results are reviewed here with the hope of clarifying some of the major issues in the field. In addition, an article expressing concerns regarding some of the early trials is described.
**TIME**

The Timing in Myocardial Infarction Evaluation “TIME” trial is a multicenter 2 by 2 randomized, placebo controlled trial performed as part of the Cardiovascular Cell Therapy Research Network (CCTRN) sponsored by the National Heart Lung and Blood Institute (NHLBI). The objectives of the trial was to determine the effect of timing of intracoronary injection of $1.5 \times 10^8$ autologous BM derived cells on recovery of Left Ventricle (LV) function after successful primary Percutaneous Coronary Intervention (PCI) for anterior ST-Elevation Myocardial Infarction (STEMI). Overall, 120 patients were recruited. The inclusion criteria included patients with an ejection fraction equal to or less than 0.45 after PCI. Cells were injected 3 or 7 days after PCI. The primary end points were global and regional LV function at 6 months after treatment.

This is a very well designed trial representing real life conditions encountered in many centers. In spite of the relatively small number of patients dealt with in each center, the trial is likely to influence practice by dampening some of the prevailing enthusiasm for infusing unmodified BM mononuclear cells into the coronaries at 3 or 7 days after MI. Indeed, no significant influence in either treatment group versus placebo on both end points was observed.

**SWISS-AMI**

The four-month results of this trial were published in *Circulation* earlier this year. Like TIME, SWiss multicenter Intracoronary Stem cells Study in Acute Myocardial Infarction (SWISS-AMI) trial was designed to examine the effect of timing of intracoronary injection of 10 mL of mononuclear BM derived cells at different interval, 3–4 days or 5–7 weeks after successful primary PCI. The authors randomized 200 patients to controls, early and late cell infusion. The primary end point was left ventricular function determined by cardiac MRI, at different time points. The current publication relates to the 4 month results. At this point, there was no difference in the primary end point between the three groups. Although the period of follow up was very short, the findings confirm those of the TIME trial.

**CELLWAVE**

This trial was designed to test the possible beneficial effect of application of shock waves to the heart 24 h before intracoronary infusion of BM derived cells in patients with chronic post infarction HF. The authors randomized patients to placebo ($n = 20$), high dose ($n = 40$) and low doses ($n = 42$) shock waves. The primary endpoint was to assess a change in global left ventricular ejection fraction (LVEF), measured at 4 months after treatment. They observed a modest improvement in LVEF from 1% in the placebo group to 3.5% in the shockwave + BM-MSCs group. Regional wall thickening also improved modestly from 0.5% in the placebo group to 3.6% in the shockwave + BM-MSCs group. This trial highlights the need for additional modalities to improve the results of these procedures.

**POSEIDON**

This early trial of PercutaneOus StEm cell Injection Delivery effects On Neomyogenesis (POSEIDON) examines the use of autologous versus allogenic BM-MSCs injected into the myocardium through the trans endocardial route in patients with post myocardial infarction HF. The authors randomized patients (5 in each group) to autologous versus allogenic MSCs, in the absence of a control group. The endpoints were a combination of clinical and hemodynamic parameters with emphasis on safety profile at one month. The results showed that both types of cells were safe and produced comparable improvements in endpoints, with little evidence of an immune reaction to the allogenic cells. Another interesting finding in this trial was the benefit of injection of a smaller number of cells (20 million) was superior to larger numbers (100 – 200 million). This proof of principle trial suggest that the use of “off the shell” allogenic MSCs might be feasible in the future, and strengthens the need for processing BM derived cells before injection.

**C-CURE**

The Cardiopoietic stem Cell therapy in heart failURE (C-CURE), is a multi-center randomized placebo controlled trial of feasibility, safety and efficacy of BM derived cardiopoietic mesenchymal stem cells use in post myocardial infarction chronic HF. BM was harvested and isolated mesenchymal stem cells were exposed to a cardiogenic “cocktail”. The cells were injected through the endocardium using a Nog catheter (Medtronic). The end point was a composite score incorporating several hemodynamic and clinical parameters.
Overall, 21 patients received the cell therapy and 15 acted as controls. Strict quality control and testing for beginning myocardial differentiation was performed. The ejection fraction improved by 7% and the left ventricular end-systolic volume was reduced by 16 mL in the treatment group as compared to no change in the placebo. Similarly, there was improvement in the composite score in the treatment group. This trial is a model of what can be done in this field. Longer term results of this trial and similar trials are awaited with great interest.

**DISCUSSION**

Although the use of unprocessed BM derived cells for regenerative therapy is extremely attractive because of availability and the short time required for its preparation, the collective evidence from the
trials discussed above and previous clinical trials (elegantly reviewed in a meta-analysis of 33 trials)\(^\text{38}\) strongly suggests that we must move on.

We are awaiting with great interest the results of additional ongoing clinical trials such as: the Transendocardial Autologous Cells (hMSC or hBMC) in ischemic Heart Failure Trial (TAC-HFT),\(^\text{29}\) PROspective randomized study of MEsenchymal stem cell THerapy in patients undergoing cardiac Surgery (PROMETEUS), POSEIDON-DCM (studying MSCs therapy for the treatment of idiopathic dilated cardiomyopathy) and the larger scaled phase II intracoronary reinfusion of Bone marrow-derived mononuclear cells (BM-MNC) on all-cause mortality the in Acute Myocardial Infarction (BAMI) trial.

Though, the overall results of the large number of clinical trials already performed suggest that even if proven safe, and when using allogeneic MSCs, modest improvement of patient condition sustained on long term is observed. Procedures designed to enhance the performance of these cells seems therefore to be warranted. Four main areas of research could be actively pursued. As far as HSCs are concerned, new solutions have been developed recently for HSCs in vitro amplifications and should be further tested for heart failure treatment.\(^\text{30}\)

As for MSCs, pre-treatment of the cells and there reprogramming towards cardiac fate prior to injection seems be the direction of choice based on the better results observed with C-CURE. New modifications via genetic alteration or Wnt and TGF-\(\beta\) pathway targeting could be further pursued. BM-MSCs might also not be the candidate of choice for heart therapy, and alternative source of MSCs could be tested. Indeed MSCs can be isolated from a broad array of tissues (not exhaustively: adipose tissues, cord blood, placenta etc.) that present acute hematopoiesis.\(^\text{32}\) Nevertheless, the same restricted improvement might also be seen with these MSCs. Evidence of pre-clinical and clinical data suggest that most of the beneficial effect of BM-MSCs treatment rely on their paracrine effects more than direct cardiomyocyte differentiation. In that case, and considering the safety of their injection and the immuno regulatory effect, MSCs use could be rethought as a complement to other cell based therapies (like cardiac stem cells). Indeed, as stressed in the previous issue of the Journal,\(^\text{35}\) alternative methods using cardiac derived stem cells, exploiting the self-renewal capacity of the differentiated myocardial cell, or cell reprogramming must be actively pursued.

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