Commentary

The modest outcome of clinical trials with bone marrow cells for myocardial repair: is the autologous source of cells the prime culprit?

Muhammad Siddique Shahid*, Wael Lasheen*, Khawaja Husnain Haider

Sulaiman Al Rajhi Medical Colleges, AlQaseem, Buraidah, Kingdom of Saudi Arabia

*These authors contributed equally to this work.

Correspondence to: Khawaja Husnain Haider, MPharm., PhD. Professor, Cellular and Molecular Pharmacology, Department of Basic Sciences, Sulaiman Al Rajhi Medical Colleges, Alqaseem, Sulaiman Alrajhi Medical College, AlQaseem, Buraidah, Kingdom of Saudi Arabia. Email: kh.haider@sr.edu.sa.

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Re-entry of cardiomyocytes into cell cycle and participation of the resident cardiac stem cells (CSCs) as part of the intrinsic repair process have been evidenced in the ischemic heart (1-3). Nevertheless, the inadequacy of these mechanisms of intrinsic repair necessitates outside intervention especially when the damage inflicted is massive in terms of the loss of functional myocytes. The situation is further aggravated by the advanced age of the patients with ischemic heart disease, and the complexity of the disease process which renders the tissue environment in the diseased heart more intimidating for the transplanted cells besides impacting the stemness characteristics and reparability of the intrinsically available stem cells (4). Since the publication of earlier reports encompassing *in vitro* experiments and the pre-clinical studies that showed cardiogenic potential of bone marrow (BM) derived stem and progenitor cells in experimental settings (5,6), these cells have been extensively assessed for reparability of the damaged myocardium in numerous clinical trials. Although the success story about BM cells for myocardial regeneration and repair spans over one and a half decade, it has been recurrently plagued by controversies about their potential to differentiate into morphofunctionally competent cardiomyocytes (7,8). Likewise, divergent with the results of the earlier clinical studies which were encouraging in terms of both safety and efficacy, subsequent trials had implied therapeutically nominal and statistically non-significant therapeutic benefits. A recent meta-analysis based on data of 2,604 patients from 48 randomized controlled trials shows improved left ventricle ejection fraction (LVEF) [2.92%; 95% confidence interval (CI), 1.91–3.92; P<0.00001] and attenuated infarction size (–2.25%; 95% CI, –3.35 to –0.95; P=0.0007) despite exclusion of studies with discrepant outcome reporting (9). Moreover, the meta-analysis reports improved outcome in terms of improved LVEF, left ventricle end systolic volume (LVESV) and left ventricle end diastolic volume (LVEDV) when cell transplantation was carried out earlier; between 3 and 10 days after infarction episode. Nevertheless, akin to several other recent studies (10,11), notably the ones reporting long-term follow-up, the data published by Sürder *et al.*, from University Hospital, Zurich, Switzerland reports no significant change in global cardiac function after transplantation of BM derived mononuclear cells (BM-MNCs) during 12 months follow-up. The multi-centre study (http://www.clinicaltrials.gov.; unique identifier: NCT00355186) involved 200 patients with ST-segment elevation myocardial infarction (MI) who were successfully re-perfused by percutaneous coronary intervention (PCI). The patients were randomized to receive BM-MNCs at two stipulated time-points of 4–7 days and 3–4 weeks after MI whereas the control group received no cell therapy. The randomized study was designed as 1:1:1 for control and the two experimental groups and, was performed immediately after PCI in the culprit coronary artery to ascertain the optimal time of cell transplantation after MI and its impact on the outcome of the procedure (12). The same group of researchers have previously published 4-month follow-up data from the SWISS-AMI study which also showed little change in the LVEF in both early and late treatment

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groups in comparison with the non-treated control group of patients (13). Cardiac magnetic resonance (CMR) imaging combined with NT-ProBNP was used to assess the functional outcome of the treatment. Incidentally, CMR imaging has emerged as the gold standard to assess the dynamic changes in ventricular structure and function in relation to the LV-remodelling after ischemic injury and offers high spatial and contrast image resolution. LV-remodelling both in terms of global LV-volumes as well as regional wall abnormalities were studied using indices of cardiac function i.e., LVEF, LVEDV, and LVESV. Availability of longitudinal data sets in the study at baseline, 4 and 12 months allowed effective and accurate assessment and prediction of progression of LV-remodelling and heart failure. Likewise, the gradient-(recalled)-echo sequence used in the study is a versatile imaging modality and is especially useful for functional, perfusion and angiographic imaging. The use of conventional extracellular gadolinium-chelates contrast medium as a part of the CMR protocol allowed reliable assessment of myocardial perfusion, function and the evolution of scar tissue. Conversely, NT-proBNP, a highly sensitive and specific biomarker of LV-dysfunction and a reliable predictor of prognosis (14), was the only parameter that pointed towards beneficial effect of the BM-MNC therapy in both the "early" and the "late" treatment groups at month 4 and staying elevated in the control group even at 12 months of treatment. The data thus generated was analysed to determine changes in different end-points including LVEF, LVEDV, LVESV, NT-proBNP values between the three treatment arms over time, i.e., between baseline, 4 months and 12 months using a multivariable linear regression model for repeated measures. Treatment arms were compared at baseline using the Kruksal Wallis test and the Fisher exact test for continuous and categorical data respectively (12). However, it is unclear which statistical tests were applied to analyse the data where combined events were calculated. Since the baseline values of LVEF and NT-ProBNP were different between groups, the comparison of absolute change in value is vague. Contemplating the number of patients reported in the different analyses, none has the initial number of randomized patients and only those patients who completed the study protocol have been included in the analysis. These observations combined with the understandably high patient drop-out rate, and exhaustive data imputation are suggestive that the study may be categorized as per protocol analysis averse to its initial design as an intent-to-treat analysis (15).

While discussing the study limitations, Sürder *et al*. have rightly pointed out that the researchers in the field of stem cells are still uncertain about many of the fundamental issues ranging from the best cell type to the optimal time after MI for cell-based therapy despite more than decade-long efforts in the clinical settings (12). The autologous availability of the BM cells is considered as one of the major advantages associated with their use for cell-based therapy and hence, transplantation of autologous BM cells remains a communal feature of most clinical studies reported to date. Given that the volunteers enrolled in the clinical studies are predominantly elderly patients, the quality of the autologous BM cells used for transplantation and the impaired "stemness" BM cells due to physiological aging might be the prime factors that impact these studies in terms of modest outcome. A direct comparison of the transcriptional profiling of the rodent BM stem cells derived from young (range, 8–12 weeks) and aging (range, 24–28 weeks) donor rats was performed to address this important issue of physiological aging (16). *In vitro* studies showed that the BM cells derived from the young donors were less responsive to the apoptotic stimuli and secreted higher levels of angiogenic growth factors under hypoxic conditions as compared to their counterparts from the aging donors. For head–to-head comparative fate determination *in vivo* and reparability assessment, experimental animal studies using rat heart model of acute left anterior descending coronary artery ligation was developed and the young and aging BM cells (labeled with different cell tracking dyes) were transplanted in the infarcted heart of the same young recipient. Histological studies revealed that the young BM cells survived and differentiated better than their old counterparts in the same heart. We inferred that the young BM derived cells might provide a better option for cell transplantation therapy because physiological aging caused significant impairment of BM stem cell characteristics, their differentiation potential as well as paracrine activity. An interesting aspect of our data was that even the tissue environment of young recipient heart failed to recuperate the impaired functionality of physiologically old donor cells. If that also holds true in the humans, it is quite expected that transplantation of autologous BM-MNCs from aging patients into their own aging, diseased heart may not procure better prognosis. Our subsequent study with neonatal, young and old BM derived stromal cells showed physiological aging associated cellular senescence of old BM stromal cells in terms of growth curves, proliferation capacity, clonogenicity and neuropeptide Y receptor

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expression (17). Our mechanistic studies revealed that cellular senescence of the old BM cells can be alleviated by transgenic overexpression of neuropeptide Y5 in the cells followed by treatment with recombinant NPY5. In another interesting study, reconstitution of the BM in old mice with the BM from young donor mice not only led to micro-chimerism in the aged heart as was evident from the presence of young resident CSCs that persisted for 1 year of observation, these cells also participated in the repair process in the event of MI (18). The study was based on the hypothesis that young hearts retained a population of resident CSCs with myeloid, mesenchymal and mesodermal potential that was important for recovery in the event of myocardial injury. These cells become dysfunctional with physiological aging thus compromising the repairing capability of the aged heart in the event of myocardial injury. Sürder's group has also demonstrated impaired paracrine activity in the aging cells which could be rectified by reprogramming of the cells with longevity determining genes (19). Put together, these experimental data imply the importance of in-depth functional characterization of the autologous cells especially from the elderly patients prior to use for transplantation therapy rather than mere surface marker analysis and percentage viability of the cell preparation. In this regard, a basic criterion should be established for uniform functional assessment of the cell preparations for use in future clinical trials. Unfortunately, the authors of SWISS-AMI study ignored their own observations of impaired functionality of the aging cells besides neglecting the other relevant published data during designing of their clinical study. Similarly, although Afzal *et al*. has mentioned various cell relevant factors that impact the outcome of BM cell transplantation in their meta-analysis (9), the analysis falls short of considering how many studies actually performed functional assessment of the autologous cells from patients prior to implantation. The published literature at a glance reveals that majority of the clinical studies do not deem it necessary to assess the cells for functional competence, and at the most merely rely on surface marker expression and viability determination before injecting the cells into the infarcted myocardium with "hope for the best".

In conclusion, it is imperative to optimize cell therapy conditions in relevant translational studies whereas due consideration should be given to the published data stemming from the translational experimental models during designing of future clinical trials to ensure such that caveats in the cell therapy approach should be addressed to achieve the desired prognosis. The use of allogenic BM stem cells from young donors may help to overcome the limitations of aging impaired BM stem cells in the elderly patients and facilitate to improve the as yet modest outcome of the clinical trials.

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Footnote

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