Reviewer's report

Title: Rationale and design of a prospective, randomised study of retrograde application of bone marrow aspirate concentrate (BMAC) through coronary sinus in patients with congestive heart failure of ischemic etiology (The RETRO study)

Version: 0 Date: 06 Oct 2018

Reviewer: Khawaja Haider

Reviewer's report:

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Dr Pleva and Colleagues have submitted rationale and design of a prospective study entitled "Rationale and design of a prospective, randomised study of retrograde application of bone marrow aspirate concentrate (BMAC) through coronary sinus in patients with congestive heart failure of ischemic etiology (The RETRO study)". The study is intended to include 40 patients who will be divided in to two groups of control (without treatment) and experimental group (who would be treated with bone marrow aspirate by retrograde coronary infusion) for myocardial cell therapy. I have following comments:

1. The inclusion criteria states that the patients included in the study would be 18 years or older in age. Such inclusion criteria will include a diverse age group of patients. How can the researchers would compare autologous transplantation of young autologous cells from a (for example) 30 year old patient injected into a young recipient heart of 30 years as compared to another patient included in the study who would be (for example) 75 years of age (75 years aging donor cells in to a 75 years aging heart). Please refer to a recently published Paper in Regenerative Medicine 2018; 13(4), 457-75 and discuss your proposed inclusion criteria in the light of this paper. There is plenty of evidence in literature that aging of the donor is associated with declined function of the donor cells in cell therapy (For example, please refer to "Aging is associated with decreased maximal life span and accelerated senescence of bone marrow stromal cells. Bone 33(6), 919-926 (2003).

2. Quality of cell preparation remains fundamental to any cell therapy procedure. The authors have not mentioned any quality control of their cell preparation, not even to measure the cell viability. (Please refer to the article: "The modest outcome of clinical
trials with bone marrow cells for myocardial repair: is the autologous source of cells the prime culprit? J. Thorac. Dis. 8(10), E1371-E1374 (2016)." Please take into serious consideration how can you have good and uniform quality of cell preparation in all patients included in the study.

3. The number of cells to be injected is a critical factor that would determine the outcome of the cell therapy procedure (as discussed by the authors in their discussion section). However, the cell preparation for injection would be based solely on volume of cell preparation and not the number of cells. Thus, it is anticipated that the number of cells injected in each patient would be different. Therefore, it would be highly difficult to compare the effect of cell therapy in patients in the treatment group who had received same volume of cell preparation but containing different cell number.

4. The composition of the cell preparation in terms of constituent cell population should be determined in terms of BM cells (surface markers for hematopoietic and non-hematopoietic populations), platelets, granulocytes etc. As the authors of the study design are anticipating the role of cytokine and growth factors (bioactive molecules) secreted by these constituents of their cell preparation, it would be prudent to characterize the cell preparation for each patient.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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