Author's response to reviews

Title: Intravenous transplantation of mesenchymal stem cells preconditioned with early phase stroke serum: Current evidences and study protocol for a randomized trial

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Author's response to reviews: see over
We would like to submit the manuscript entitled “Intravenous transplantation of mesenchymal stem cells preconditioned with early phase stroke serum: Current evidences and study protocol for a randomized trial” for consideration of Trials.

We have done our best to respond to the reviewer's invaluable comments.

Sincerely,

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Reviewer's report

Title: Intravenous transplantation of mesenchymal stem cells preconditioned with early phase stroke serum: Current evidences and study protocol of a phase 3 randomized trial

Version: 1 Date: 11 July 2013

Reviewer: Erik Cobo

Reviewer's report:

I read the paper from Suk Jae Kim et al., “Intravenous transplantation of mesenchymal stem cells preconditioned with early phase stroke serum: Current evidences and study protocol of a phase 3 randomized trial”, and I think it is suitable for publication in Trials.

But before recommending publication, I would like authors to address the suggestions indicated below. Thank you very much for considering our journal and looking forward to see a new version of your manuscript.

Erik Cobo.

Response: Thanks for your invaluable comments.

- Major Compulsory Revisions
Commnet#1: I’m confused about the confirmatory nature of the trial (abstract: “The results have implications for the development of evidence-based best practices”; and trial characteristics: “phase 3”) and so many unknowns (second section, optimization of treatment: “The appropriate type and dose of cells, the mode of treatment, and the time of application of stem cell therapy remain to be determined.”). Please, define clearly your trial as confirmatory (“pivotal”) or exploratory (“pilot”) and write your report accordingly.

Response: Thanks for the comment. Although we previously performed two pilot studies using MSCs in patients with large stroke [Ann Neurol, 2005; Stem Cells, 2010], the protocol of this study is somewhat different from the previous ones in some aspects, including selection of patients and methods of MSCs culture and injection. Therefore, as the reviewer’s point, we also think that the nature of our trial is close to the exploratory study rather than the confirmatory research. In this regard, the manuscript has now been changed accordingly (title, abstract, and main body).

Comment#2: According to your title (“current evidences”), please update table 1 with information about the results of the studies. Ideally, a summary effect size with its imprecision should be provided.
Response: The reviewer’s point is well taken. In table 1, we already summarized the results (efficacy and adverse event) of previous works. Unfortunately, the effect size cannot be provided because most of the studies had no control group and they used different primary outcomes.

Comment#3: The masked evaluator (if blinding is not broken) can protect against evaluation bias, but open trials also have other risks of bias, such as selection, performance and attrition. Please, provide arguments to prevent such biases.

Response: The reviewer’s point is well taken. First, to avoid selection bias, patients will be randomly assigned to each group, and potential confounders that may influence our results including age, sex, stroke mechanisms, and infarct volume will be adjusted (page 15 and 16). Second, to minimize performance bias, conventional treatments including medications and rehabilitation therapy will be provided equally according to the guidelines proposed by American Stroke Association and Korean Stroke Society. Lastly, to avoid attrition bias, an intention-to-treat analysis will be used for the comparison between groups (page 16).

Comment#4: Some key information is missing from the abstract (i.e., sample size) and
the report (i.e., allocation concealment). Please, check with the SPIRIT statement to ensure that you provide all essential features of the trial. [Please, be aware that your future final report should be in accordance with the CONSORT statement and also with its extension for non-pharmacologic interventions.]

Response: Thanks for the comment. The abstract has now been changed.

Commnet#5: The previous STARTING trial, with a sample size of 85 patients, failed to find statistical significance. Please, provide arguments why your new smaller trial (60) will prove to have a beneficial effect (for example, higher expected effect, more powerful main analysis, more homogeneous population, better reliability in outcome determination, …).

Response: The reviewer’s point is well taken. The reasons of that are a) we will only include patients who have less damage in periventricular areas, as improvement in functional outcome was consistently observed only in these subjects in STARTING-1; b) improving efficacy of MSC therapy will be expected due to ischemic preconditioning and BBB manipulation; c) we will use a categorical shift analysis in mRS as the primary endpoint which has advantage over the classical dichotomized method for interventions
that confer a uniform and modest benefit to patients over a broad range of stroke severity like this trial.

In addition, assumptions underlying the sample size calculation will be adjusted by an interim analysis performed by an independent data and safety monitoring committee (data from 20 eligible participants in the MSC group) [Adaptive design].

**Comment#6:** Please, specify which will be the main analysis (unadjusted CMH or adjusted ordinal logistic regression).

**Response:** Thanks for the comment. As mentioned in page 16, the adjusted result is prespecified as the primary outcome analysis.
- Minor Essential Revisions

- Discretionary Revisions

Please note that ‘optimal’ refers to some criteria. Please, consider either specifying such criteria or removing the term ”optimal” from some places.

Response: Thanks for the comment. The term “optimal” has now been removed.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Response: English editing was already done by eWorld Editing (www.eworldediting.com). In addition, minor corrections have now been done during the revision period.

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: None
Editorial requests:

1) Please ensure the title conforms to journal style for study protocol articles. The title should follow the format “__________: study protocol for a randomized controlled trial.”

Response: The title has now been changed as the editorial comment.

2) Please include the authors contributions section, the competing interest section and the acknowledgements section at the end of the manuscript, not after the manuscript.

Response: It has now been changed.

3) Please remove the conclusions section, this is not needed for a protocol.

Response: It has now been modified.

4) Please include a trial status section. This should state the status of the trial at the time
of manuscript submission. The journal considers study protocol articles for proposed or ongoing trials provided they have not completed patient recruitment at the time of submission.

Response: The status of our trial has now been stated.

5) Please mention each author individually in your Authors’ Contributions section. We suggest the following kind of format (please use initials to refer to each author’s contribution): “AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.”

Response: It has now been changed.