Author's response to reviews

Title: A Multicenter, Prospective, Randomized, Controlled Trial Evaluating the Safety and Efficacy of Intracoronary Cell Infusion Mobilized with Granulocyte colony-stimulating factor and Darbepoetin after Acute Myocardial Infarction: Study Design and Rationale of the 'MAGIC Cell-5-Combination Cytokine Trial'

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Author's response to reviews: see over
To Editor of ‘Trials’

Subject: Submission of manuscript entitled “A Multicenter, Prospective, Randomized, Controlled Trial Evaluating the Safety and Efficacy of Intracoronary Cell Infusion Mobilized with Granulocyte colony-stimulating factor and Darbepoetin after Acute Myocardial Infarction: Study Design and Rationale of the MAGIC Cell–5–Combination Cytokine Trial”.

Dear Editor,

I, on behalf of the authors, would like to submit a manuscript entitled, “A Multicenter, Prospective, Randomized, Controlled Trial Evaluating the Safety and Efficacy of Intracoronary Cell Infusion Mobilized with Granulocyte colony-stimulating factor and Darbepoetin after Acute Myocardial Infarction: Study Design and Rationale of the ‘MAGIC Cell–5–Combination Cytokine Trial’” for possible publication in the Trials.

Stem cell therapy has a potential to improve cardiac function in patients
with myocardial infarction. However the degree of improvement by current stem cell treatment in myocardial infarction is limited and needs to be enhanced. To enhance the therapeutic efficacy of stem cell therapy, newer strategies should be developed.

This paper describes the ‘MAGIC Cell–5–Combination Cytokine Trial’, a proposed study to investigate the safety and efficacy of a novel stem/progenitor cell therapy for patients who have experienced acute myocardial infarction. We have successfully carried out a series of clinical trials, named MAGIC Cell trials, in which we evaluated stem/progenitor cell therapy using intracoronary infusion of mobilized peripheral blood stem/progenitor cell therapy by G-CSF in patients with acute myocardial infarction [Lancet 2004;363:751-6, Circulation 2006;114:I145-51]. In MAGIC Cell 1 and 2 trials, we confirmed the feasibility and safety of the intracoronary infusion of the mobilized peripheral blood stem cells with G-CSF in patients with myocardial infarction. But we also found the potential adverse effect of cytokine, G-CSF, to aggravate neointimal hyperplasia of bare metal coronary stents. Thus we launched MAGIC Cell-3-DES trial where we used drug-eluting stents (DES) to solve the potential side effects of cytokines which was used for mobilization of bone marrow stem cells to
peripheral blood. We confirmed the therapeutic efficacy of intracoronary infusion of the mobilized peripheral blood stem cells with G-CSF in improving left ventricular ejection fraction assessed by cardiac MRI, in comparison with the control conventional treatment group. But the magnitude of LVEF improvement was limited, although it was statistically significant. This is the reason why we decided to launch MAGIC Cell-5-Combination Cytokine Trial.

‘MAGIC Cell–5–Combination Cytokine Trial’ will evaluate a novel combination treatment of intravenous darbepoetin plus intracoronary infusion of mobilized stem/progenitor cells by G-CSF, in comparison with conventional treatment or stem cell therapy using G-CSF alone in patients with ST segment elevated acute myocardial infarction. In Phase I of the study, we will compare 3 groups; (1) the control group, (2) the G-CSF group that will receive intracoronary infusion of mobilized stem/progenitor cell by G-CSF, and (3) the combi-cytokine group that will receive the intravenous darbepoetin and intracoronary infusion of mobilized stem/progenitor cell by G-CSF. Darbepoetin and G-CSF, separately, have their own cytoprotective effects and stem cell mobilizing capacities resulting in the improvement of angiogenesis and cardiac function. Combination of them could show additive effects through separate and
independent action mechanisms to each other. And phase II of this trial will evaluate repeated stem/progenitor cell therapy in patients with persistent LV systolic dysfunction after initial stem/progenitor cell therapy. Here, we outline the proposed study and provide a review of the current literature to explain the rationale behind our methodology.

Briefly, we think that our manuscript has the following strong points which rationalize that it should be published in 'Trials';

1) The current trial is the first multicenter prospective, randomized, double-blinded (between two stem/progenitor cell therapy groups), placebo-controlled trial to evaluate the efficacy and safety of new strategy of stem/progenitor cell therapy with G-CSF and darbepoetin. It will provide an answer to the question whether the combination use of two cytokine (G-CSF and darbepoetin) in short duration is safe in human.

2) It will also provide the answer to the question whether there are additive effects with combination use of G-CSF and darbepoetin for improvement of LV systolic function in STEMI.

3) By the phase II treatment, the current trial will give insight to the question
whether repeated stem cell therapy is safe and effective.

4) Taken together, 'MAGIC-5-combination cytokine trial' would be an important study to give answers to several key issues regarding stem/progenitor cell therapy for the patients with STEMI. Thus the information of the trial design would be very valuable for the readers of ‘Trials’.

Disclosure:

1. This paper is not under consideration elsewhere.

2. None of the paper's contents have been previously published.

3. All authors have read and approved the manuscript.

4. Any of the authors have no relationship with industry.

We added requested document from editorial office including the unconditioned ethics approval document and funding documents as supplement files. Unfortunately documents are written in Korean language. So we briefly explain the status of IRB approval and grant in summary document.

All of authors actively participated in design of this study, drafting or
revising of manuscript and finally approved the submitted manuscript. We hope that our report may be fruitful to the potential readers of ‘Trials’.

Thank you in advance for considering our paper.

Best regards,

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