Safety and efficacy of intracoronary infusion of mobilized peripheral blood stem cell in patients with myocardial infarction: MAGIC Cell-1 and MAGIC Cell-3-DES-trials

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Previous clinical studies evaluating granulocyte-colony stimulating factor (G-CSF)-based stem-cell therapy showed inconsistent outcomes. We evaluated G-CSF-based stem-cell therapy in patients with acute myocardial infarction (AMI) and old myocardial infarction (OMI) in ‘Myocardial Regeneration and Angiogenesis in Myocardial Infarction with G-CSF and Intracoronary Stem Cell Infusion (MAGIC Cell)’ trials. In MAGIC Cell-1 trial, intracoronary infusion of mobilized stem cell by G-CSF is superior to G-CSF alone for improvement of left ventricular (LV) systolic function till 2 years follow-up. In MAGIC Cell-3-Drug eluting stent (DES) trial, cell infusion showed better improvement of LV systolic function and remodelling than control in AMI patients at 6 months follow-up. However, stem-cell therapy does not improve LV systolic function in OMI patients. G-CSF-based stem-cell therapy does not aggravate de novo progression of atherosclerosis while DES efficiently prevents G-CSF-based stem-cell-therapy-related restenosis. Longer-term follow-up is required to confirm prognostic impacts of stem-cell therapy in patients with myocardial infarction. Combination strategy with stem cell therapy with cytokines and genes should be introduced to enhance efficacy of current stem-cell therapy.

KEYWORDS
Myocardial infarction; G-CSF; Peripheral blood stem cell

Introduction
Therapeutic application of granulocyte-colony stimulating factor (G-CSF) for stem-cell therapy has been evaluated by preclinical and clinical trials.¹⁻⁴ In addition to well-known, stem-cell mobilizing effects of G-CSF, G-CSF also has several beneficial effects on salvage and healing of infarcted myocardium.⁵,⁶ Although most of preclinical studies showed favourable outcomes for improvement of cardiac function with G-CSF-based stem-cell therapy, results from clinical trials were inconsistent and rather disappointing.²⁻⁴ We evaluated G-CSF-based stem-cell therapy in clinical trial since 2003 in ‘Myocardial Regeneration and Angiogenesis in Myocardial Infarction with G-CSF and Intracoronary Stem Cell Infusion’ (MAGIC Cell) trials.²⁻⁹ In this article, we will present our data from clinical and preclinical studies and discuss the lessons from clinical trials and future directions of stem-cell therapy.

Findings from MAGIC Cell trials
MAGIC Cell-1 trial is a randomized controlled trial to evaluate the safety and effects of G-CSF-based stem-cell
therapy on improvement of left ventricular (LV) systolic function in patients with myocardial infarction. In MAGIC Cell-1 trial, patients were randomized into one strategy among three: (i) G-CSF mobilization alone after PCI ($n = 10$); (ii) intracoronary infusion of mobilized peripheral blood stem cell (PBSC) by G-CSF after PCI ($n = 10$); and (iii) control PCI alone ($n = 10$).7–9 G-CSF was administered at a dose of $10 \mu g/kg/day$ for 4 days before coronary stent implantation. To our knowledge, this is the only study to directly compare the strategy of G-CSF mobilization alone and that of intracoronary infusion of mobilized PBSCs. Enrolment of this study was terminated early due to concerns that G-CSF-based stem-cell therapy might increase restenosis after coronary stent implantation. However enrolled patients were followed till 2 years after randomization. During 2 years follow-up evaluation, patients in the intracoronary cell infusion group showed better improvements of LV systolic function and remodelling compared with patients in the G-CSF alone group. Discrepancy in outcomes between G-CSF alone and intracoronary cell infusion group might come from differences in retention efficacy of stem cells to infarcted myocardium.10 Patients who received intracoronary cell infusion showed selective retention of infused stem cells, but patients who received intravenous infusion of stem cells did not (retention rate 2 h after intracoronary infusion vs. intravenous infusion = 1.5 ± 0.8 vs. 0 ± 0% of infused PBSCs). Change of LV systolic function and volume was measured by myocardial SPECT. On the basis of the results from MAGIC Cell-1 trial, we decided not to evaluate G-CSF mobilization-alone strategy in the next-phase larger randomized clinical trial named MAGIC Cell-3-Drug eluting stent (DES) trial.9

In MAGIC Cell-3-DES trial, we evaluated efficacy of intracoronary infusion of mobilized PBSC in patients with acute myocardial infarction (AMI, cell infusion vs. control: $n = 27$ vs. $n = 29$) and old myocardial infarction (OMI, $n = 20$ vs. $n = 20$). Change of LV systolic function and volume was measured by cardiac MRI at 6 months follow-up. After revascularization with DES for culprit coronary vessels, patients in the cell-infusion group received 3 days of $5 \mu g/kg$ G-CSF twice daily. Then PBSC was collected and infused via intracoronary balloon catheter. In AMI patients, the cell infusion group showed better improvement of LV systolic function (change of LV ejection fraction: $+5.1 \pm 9.1$ vs. $-0.2 \pm 8.6\%$, $P < 0.05$) and remodelling (change of LV end-systolic volume: $-5.4 \pm 17.0$ vs. $+6.5 \pm 21.9 \text{mL}$, $P < 0.05$) compared with the control group.9 Cell infusion also reduced infarcted myocardial volume measured by late enhancement ($P = 0.01$) and restored LV synchronous contraction measured by Doppler tissue imaging ($P < 0.05$, unpublished data) in AMI patients.9 However control group did not show improvements. In contrast to AMI patients, no differences in change of LV systolic function and remodelling was observed between the control group and the cell infusion group in OMI patients. However cell infusion improved microcirculatory function measured by coronary flow reserve (baseline vs. follow-up: $1.97 \pm 0.60$ vs. $2.70 \pm 0.88$, $P < 0.01$) and reduced infarcted myocardial volume measured by late enhancement ($P = 0.06$) in OMI as well as AMI patients.9

No improvement was observed in OMI control group.

Regarding the safety issues, G-CSF-mediated inflammation and restenosis can be discussed. In MAGIC Cell-1 trial, we suggested potential risk of G-CSF-mediated restenosis in patients with myocardial infarction (restenosis rate of G-CSF group vs. cell infusion group vs. control = 50 vs. 50 vs. 30%, $P = 0.375$).

We evaluated underlying mechanisms of G-CSF-mediated restenosis and tested paclitaxel eluting stents as a preventive measurement in animal study.11 Animal experiments showed that paclitaxel eluting stent can prevent G-CSF-mediated neointimal growth and G-CSF can enhance endothelial recovery of drug eluting stent. On the basis of the results of animal study, we adopted DES exclusively in MAGIC Cell-3-DES trial. At 6 months follow-up of MAGIC Cell-3-DES trial, no differences in the development of restenosis and de novo progression of atherosclerosis were observed between the cell infusion group and the control group. Although G-CSF can mildly aggravate inflammation in patients with myocardial infarction, G-CSF did not increase the risk of myocardial ischaemia and did not deteriorate endothelial function measured by flow-mediated dilation (unpublished data). Recently, Steinwender et al.12 reported three cases of late stent thrombosis from a cohort of 24 patients who underwent bare-metal stent implantation and intracoronary infusion of mobilized PBSC by G-CSF. However we did not observe additional risk of late stent thrombosis in patients who received G-CSF-based stem-cell therapy in MAGIC Cell studies. Occurrence of death, myocardial infarction, and hospitalization due to angina were not significantly different between the cell-infusion group and the control group.

Lessons from MAGIC Cell trials and future directions

There are controversies whether G-CSF alone can improve cardiac function in patients with AMI. The results of MAGIC Cell trial7–9 and evaluation of retention efficacy of infused-stem cells10 strongly suggested that direct local delivery of stem cell is required to induce retention of stem cells to infarcted myocardium and improve cardiac function. Our study is insufficient to conclude effectiveness of G-CSF alone to improve cardiac function due to small sample size and heterogeneous characters of patients of the study, and relatively short duration of G-CSF treatment. However, we believe that there are evidences from lots of studies that at least intracoronary infusion of peripheral blood or bone-marrow stem cell is more reliable protective mechanisms for myocardial damage in ischaemic damage,5,6 G-CSF-mediated inflammation and its potential deteriorating effects of atherosclerotic disease may discourage long-term use of high-dose
Table 1  Clinical trials with G-CSF-based stem cell therapy in patients with acute myocardial infarction

| Design                     | G-CSF dose and duration | Numbers of infused cells | Follow-up duration (month) | Study group | Baseline left ventricular ejection fraction | Change of left ventricular ejection fraction | P-value | Evaluation of left ventricular ejection fraction |
|----------------------------|--------------------------|--------------------------|---------------------------|-------------|---------------------------------------------|---------------------------------------------|---------|------------------------------------------------|
| G-CSF vs. control          |                          |                          |                           |             |                                             |                                             |         |                                                 |
| MAGIC Cell-1,8             | Randomized open label    | 10 μg/kg/day for 4 days  | 24                        | G-CSF=10    | 53.0                                        | +0.1                                        | NS      | SPECT                                           |
|                            |                          |                          |                           | Control=10  | 44.4                                        | +6.9                                        |         |                                                 |
|                            |                          |                          |                           | Cell infusion=10 | 48.9                                        | +10.0                                       |         |                                                 |
|                            |                          |                          |                           | G-CSF=11    | NA                                          | NA                                          | NS      | SPECT                                           |
| Suzuki et al.13            | Randomized open label    | 10 days (peripheral blood leukocyte=30 000/μL) | 1             | G-CSF=11   | NA                                          | NA                                          | NS      | SPECT                                           |
| Takano et al.14            | Randomized single blinded, placebo controlled | 2.5 μg/kg/day for 5 days | 6             | Control=11 | 47.2                                        | +4.6                                        | NA      | SPECT                                           |
| Valgimigli et al.15        | Randomized single blinded, placebo controlled | 5 μg/kg/day for 4 days | 6             | G-CSF=19   | 45.6                                        | +3.4                                        | +22     | NS SPECT                                        |
| Ellis et al.16             | Randomized, double blinded, placebo controlled | 5 or 10 μg/kg/day for 5 days | 1             | Control=10 | 36.8                                        | +14                                         | NS      | Echo                                            |
|                            |                          |                          |                           | G-CSF=6     |                                             |                                             |         |                                                 |
|                            |                          |                          |                           | G-CSF=6     | 38.7                                        | +5.2                                        |         |                                                 |
|                            |                          |                          |                           | Control=6   | 33.7                                        | +8.0                                        |         |                                                 |
|                            |                          |                          |                           | G-CSF=25    | 48                                          | +6                                          | <0.001  | Echo                                            |
| FIRSTLINE-AMI3             | Randomized, open label   | 10 μg/kg/day for 6 days  | 6             | Control=25 | 51.2                                        | +8.5                                        | NS      | MRI                                             |
| STEMMI2                    | Randomized, double blinded, placebo controlled | 10 μg/kg/day for 6 days | 6             | G-CSF=37   | 47                                          | -4                                          | +8.5    | NS MRI                                          |
|                            |                          |                          |                           | Control=6   | 51.2                                        | -4                                          | +8.5    | NS MRI                                          |
|                            |                          |                          |                           | G-CSF=25    | 51.3                                        | +8.0                                        | NS      | MRI                                             |
| REVIVAL-24                 | Randomized, double blinded, placebo controlled | 10 μg/kg/day for 5 days | 6             | Control=33 | 55.7                                        | +8.0                                        | NS      | MRI                                             |
|                            |                          |                          |                           | G-CSF=56    | 51.3                                        | +0.5                                        |         | MRI                                             |
|                            |                          |                          |                           | Control=58  | 51.3                                        | +8.0                                        | NS      | MRI                                             |
|                            |                          |                          |                           | G-CSF=19    | 41                                          | +2.0                                        |         | MRI                                             |
|                            |                          |                          |                           | Control=18  | 44                                          | +5.3                                        |         | MRI                                             |

Continued
G-CSF in patients with myocardial infarction. We believed that G-CSF should be considered primarily as a stem-cell mobilizer to avoid invasive bone-marrow harvest and used the shortest duration to mobilize adequate numbers of PBSC for local cell infusion.

Effects of intracoronary infusion of mobilized PBSC by G-CSF to improve LV systolic function in AMI patients is consistent through MAGIC Cell-1 and MAGIC Cell-3-DES trials. However the degree of improvement of LV systolic function is modest, and influences on clinical outcome cannot be adequately evaluated in our studies like most of other clinical trials of stem-cell therapy. Especially therapeutic efficacy of current strategy for OMI patients was very limited and should be enhanced. There are several aspects to be considered to enhance the therapeutic efficacy. First, enhancement of retention efficacy can be a reasonable strategy. In our study, only <5% of infused cells can be observed in infarcted myocardium. Poor retention efficacy can be responsible for limited efficacy of current stem-cell therapy. We tried to develop methods to pre-treat target tissue or stem cell to enhance retention. We have evaluated the role of magnetic nanoparticles to enhance homing and retention of infused stem cells to target tissues. Secondly, improvement of stem-cell function can be achieved by pre-treatment of patients and stem cells. We have studied pre-treatment of stem cells with genes like integrin-linked kinase, glycogen synthase kinase-3beta, beta-catenin, and small molecules such as angiopoetin-1, erythropoietin, peroxisome proliferators-activated receptors agonists in preclinical studies. In early 2007, we launched a clinical trial named MAGIC Cell-5-combicytokine trial to evaluate the efficacy of combination therapy with erythropoietin and intracoronary infusion of mobilized PBSC by G-CSF to improve cardiac function in patients with AMI.

Conclusion

Intracoronary infusion of mobilized PBSC by G-CSF can improve LV systolic function and remodelling in patients with AMI. However efficacy of the current strategy of G-CSF-based stem-cell therapy should be improved especially in patients with OMI. Influences on clinical outcomes should be evaluated in longer-term follow-up study.

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