Usefulness of Hyper Early Granulocyte-colony-stimulating Factor Therapy for Patients with Acute Myocardial Infarction

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Abstract

Objective: It has been reported that granulocyte-colony-stimulating-factor (G-CSF) induces myocardial regeneration and revascularization after acute myocardial infarction (AMI) by mobilizing bone marrow stem cells and suppressing apoptosis of endothelial cells in the injured heart. This study investigated whether hyper early G-CSF therapy was beneficial for AMI patients.

Methods: Forty consecutive patients with initial ST-segment elevation AMI were randomized to receive intravenous infusion of G-CSF at 2μg/kg over 30 min (G-CSF group) or infusion of normal saline (control group) once daily for 5 days. The first dose was administered during primary percutaneous coronary intervention just after hospitalization. In the subacute period and 6 months after AMI, all patients underwent myocardial scintigraphy, including 99mTc-sestamibi imaging of myocardial perfusion and 123I-beta-methyl-piodophenylpentadecanoic-acid (123I-BMIPP) imaging to assess fatty acid metabolism.

Results: The two groups had a similar myocardial area at risk, as evaluated by the extent score on subacute 123I-BMIPP imaging. Compared with the control group, the G-CSF group had a significantly smaller (p<0.05) total defect score on 99mTc-sestamibi and 123I-BMIPP imaging at 6 months. In addition, the left ventricular ejection fraction and regional wall motion score were larger in the G-CSF group than in the control group during the subacute period and after 6 months.

Conclusions: Hyper early G-CSF therapy improves myocardial perfusion, fatty acid metabolism, and cardiac function after AMI.

Keywords: 123I-BMIPP, 99mTc-sestamibi, Acute myocardial infarction, G-CSF, Nuclear imaging

In 1997, Asahara et al. reported the isolation of putative endothelial cell progenitors or angioblasts from human peripheral blood by selection with magnetic beads, and stated that these cells underwent differentiation into endothelial cells when cultured (1). In addition, Orlic et al. reported the promotion of tissue regeneration by mobilization of bone marrow cells in transgenic mice using stem cell factor and granulocyte colony-stimulating factor (G-CSF), with cytokine-induced repair of cardiac tissue decreasing mortality by 68% and reducing infarct size by 40% (2). Moreover, Ince et al. reported that mobilization of CD34-positive mononuclear cells by G-CSF after primary percutaneous coronary intervention (PCI) improved ventricular function and prevented left ventricular remodeling at 4 months after myocardial infarction (3). A recent systematic review and meta-analysis of randomized controlled trials concluded that G-CSF therapy is safe for unselected patients with acute myocardial infarction (AMI), but does not provide any overall benefit. However, subgroup analyses suggested that G-CSF therapy may be useful for AMI patients with left ventricular (LV) dysfunction and may also be beneficial if it is started early (4).

Because administration of G-CSF mobilizes bone marrow
stem cells into the peripheral blood, the possibility of using this cytokine for noninvasive regenerative therapy has been suggested recently. G-CSF was reported to inhibit apoptosis of endothelial cells after AMI, but there have been no reports about the effects of G-CSF infusion initiated during reperfusion therapy. Accordingly, the present study was performed to clarify whether hyper early initiation of G-CSF therapy after AMI was beneficial for reducing the extent of myocardial injury on myocardial scintigraphy and improving cardiac function.

**Methods**

In March 2010, the protocol for this study was approved by the Institutional Ethics Review Board to allow use of G-CSF in a maximum of 25 patients. Written informed consent was obtained from all patients prior to enrollment and this study was performed in accordance with the precepts of the Declaration of Helsinki.

**Patients and G-CSF treatment**

Forty-two consecutive patients with acute ST-elevation myocardial infarction (STEMI) who received primary PCI with stenting were enrolled in this study between April 2010 and October 2011. The exclusion criteria were as follows: cardiogenic shock, severe valvular heart disease, serious arrhythmia, malignancy, chronic renal failure, liver dysfunction, poorly controlled thyroid dysfunction, pregnancy, anemia, and bone marrow disease. Patients were judged to have no malignancy when there was no history of malignancy and no abnormal tumor markers.

Before reperfusion, patients were randomized 1:1 by the envelop method to receive intravenous infusion of G-CSF (Gran Syring; Kirin Cooperation, Tokyo, Japan) at 2 μg/kg over 30 min or infusion of normal saline once daily for 5 days in addition to standard care. The first infusion was given during primary PCI just after admission to hospital and the peripheral white blood cell count was measured every day during infusion of G-CSF or saline. Baseline and follow-up examinations included measurement of the white blood cell count, brain natriuretic peptide, and interleukin-6. Checking to detect adverse effects of the study medication was performed every day during the treatment period.

**Coronary angiography**

All patients underwent coronary angiography according to the standard procedure at initial PCI and at follow-up. Quantitative coronary angiography was done with a Centricity Cardiology CA 1000 Ver. 2.0 and the percent stenosis was calculated.

**Myocardial scintigraphy**

Resting $^{123}$I-beta-methyl-p-iodophenylpentadecanoic acid (BMIPP) SPECT was done on the sixth day after admission and $^{99m}$Tc-sestamibi (MIBI) quantitative gated SPECT was performed on the ninth day. At 6 months after AMI, both SPECT studies were repeated and coronary angiography was also performed. All scintigraphic studies were done after a 12-h overnight fast in the absence of anti-angina medication. $^{123}$I-BMIPP was obtained from Nihon Mediphysics (Tokyo, Japan). Each patient received 111 MBq of $^{123}$I-BMIPP intravenously while sitting upright and SPECT images were acquired after 15 min. $^{99m}$Tc-MIBI was obtained from FUJIFILM Toyama Chemical Co., Ltd., (Tokyo, Japan). Each patient received 740 MBq of $^{99m}$Tc-MIBI intravenously while sitting upright and took milk or chocolate. Gated SPECT images were acquired 30 min after injection by dividing the RR interval into 16 subintervals. Imaging was performed by using an IRIX three-headed SPECT system (Picker, Cleveland, OH) with low-energy, all-purpose resolution, parallel-hole collimators.

**Analysis of SPECT data**

Each myocardial SPECT image was divided into 17 segments and regional tracer uptake was assessed semi-quantitatively by using a five-point scoring system (0 = normal uptake; 1 = mildly reduced uptake; 2 = moderately reduced uptake; 3 = severely reduced uptake; and 4 = no uptake). Then the total defect score (TDS) was calculated as the sum of the scores for each of the 17 segments, while the extent score was calculated as the number of segments with reduced uptake or defects. The myocardial area at risk was evaluated from the extent score on subacute $^{123}$I-BMIPP SPECT.

**Analysis of LV function**

The quantitative gated SPECT program (Cedars-Sinai Medical Center, Los Angeles, CA) was used to create a 3-dimensional surface cinemode display with a temporal resolution of 16 frames per RR interval. Then this display was employed with an automatic edge detection algorithm to calculate the left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV) throughout the cardiac cycle (5). Regional wall motion of segments in the area at risk was evaluated visually on resting cinemode images and a regional wall motion score (RWMS) was assigned by using a 6-point scale (−1 = dyskinesis; 0 = akinesis; 1 = severe hypokinesis; 2 = moderate hypokinesis; 3 = mild hypokinesis; and 4 = normokinesis) (6).

**Statistical analysis**

Continuous variables are presented as the mean ± SD. Categorical variables were compared by the χ² test or Fisher’s exact test. Comparison of specific parameters was performed
by the paired two-tailed t-test, while the unpaired two-tailed t-test was employed for comparisons between the G-CSF group and the control group. Analyses were done with JMP software (SAS Institute Inc., Cary, NC) on a Macintosh computer.

Results

Clinical characteristics of the study population

Two of the 42 patients dropped out during the 6-month observation period and the remaining 40 patients (31 men and 9 women aged 65 ± 9 years) were evaluated (Figure 1). Demographic and clinical characteristics of the G-CSF group and control group were similar, revealing a typical distribution of risk factors and evidence-based medications. Follow-up treatment was also similar in both groups (Table 1).

Angiographic and infarct characteristics were balanced between the two groups, and the time from the onset of symptoms to recanalization was similar (p = 0.534). There were no complications associated with PCI, and recanalization of occluded infarct-related arteries by stenting was successful in 95% of patients from each group. There were 7 patients (35%) with multivessel disease in the G-CSF group and 3 patients (15%) in the control group, with no significant difference between the two groups (p = 0.273). The two groups also showed no significant differences of collateral flow, the percentage of patients with stenting, stent diameter, and baseline TIMI grade before PCI. After PCI, TIMI 3 flow after PCI was obtained in 19 patients (95%) from the G-CSF group, which was a higher rate than in the control group, but the difference was not significant (p = 0.342). The maximum creatine kinase level was tended to be lower in the G-CSF group compared with the control group (p = 0.133) (Table 1).

The white blood cell count increased significantly during treatment in the G-CSF group compared with the control group (p < 0.0001). In both groups, the levels of interleukin-6 (a marker of inflammation) and brain natriuretic peptide were high at admission and decreased after 6 months (Table 2).

There were no in-hospital events in either group. The cumulative 1-year clinical event rate was similar in both groups.

99mTc-MIBI and 123I-BMIPP scintigraphy findings

The area of myocardium at risk was similar in the two groups based on the extent score determined by subcutaneous 123I-BMIPP SPECT. On subcutaneous 99mTc-MIBI perfusion images, the TDS tended to be lower in the G-CSF group than the control group (p = 0.063), and the TDS also tended to be lower in the G-CSF group than the control group on 123I-BMIPP fatty acid uptake.
Markers of Inflammation and BNP

| Variables         | Control (n=20) | G-CSF (n=20) | p Value | Value       |
|-------------------|----------------|--------------|---------|-------------|
| WBC (baseline)    | 9966 ± 2818    | 9666 ± 2921  | 0.743   |             |
| WBC (peak)        | 13029 ± 2871   | 23206 ± 7729 | <0.0001 |             |
| WBC (6Mo)         | 6117 ± 2081    | 6004 ± 1676  | 0.854   |             |
| IL-6 (baseline)   | 87.6 ± 188.5   | 78.6 ± 76.2  | 0.856   |             |
| IL-6 (6Mo)        | 12.6 ± 33.2    | 4.2 ± 7.5    | 0.318   |             |
| BNP (baseline)    | 184.7 ± 121.3  | 334.2 ± 379.2| 0.101   |             |
| BNP (6Mo)         | 106.6 ± 91.7   | 103.5 ± 134.5| 0.936   |             |

WBC, white blood cell; IL-6, interleukin-6; BNP, brain natriuretic peptide; 6Mo, 6 months

Systolic and diastolic LV function

In the subacute period, LVEDV, LVESV, and peak filling rate (PFR) were similar in the G-CSF group and the control group, while LVEF and the RWMS were higher in the G-CSF group. At 6 months after AMI, there was a significant (p < 0.05) increase of LVEF in the G-CSF group, and it reached 59.0 ± 1.2% (p = 0.036 vs. the control group). While RWMS improved in both groups after 6 months, it was significantly higher in the G-CSF group than the control group (p < 0.0001) (Table 4).

Two representative cases

A representative case from the control group is shown in Figure 2 (left). The patient was a 68-year-old man with broad anterior AMI. A stent was successfully implanted in the proximal left anterior descending artery. Maximum CPK was 3921 U/L.

A representative case from the G-CSF group is shown in Figure 2 (right). The patient was a 72-year-old man with broad anterior AMI. The proximal left anterior descending artery was successfully stented. Maximum CPK was 2286 U/L.

Discussion

A previous meta-analysis showed that administration of G-CSF to unselected AMI patients did not improve any clinically relevant primary endpoints, with the observed differences not achieving either statistical or clinical significance. However, it has been reported that G-CSF may be beneficial if administered in the early period (<37 hours) after AMI and PCI (4). In the present study, we investigated the usefulness of hyper early G-CSF treatment, by initiating G-CSF infusion during primary PCI just after hospitalization and performing subsequent daily G-CSF infusion for 5 days in addition to standard care. Although the initial area at risk (evaluated by the 123I-BMIPP extent score (7)) was the same in both groups, reduction of the TDS during the subacute period was greater in the G-CSF group than the control group on both 99mTc-MIBI and 123I-BMIPP images, together with a larger increase of LVEF and RWMS in the G-CSF group. The G-CSF group also showed greater reduction of the extent score and the TDS on both 99mTc-MIBI and 123I-BMIPP images at 6 months after AMI, as well as a larger increase of EF and RWMS. Among markers of salvaged myocardium, the difference of the extent score evaluated as the subacute 123I-BMIPP score minus 6 months 99mTc-MIBI score tended to be higher in the G-CSF group than the control group. These results indicate that hyper early initiation of G-CSF therapy preserved myocardial fatty acid metabolism and perfusion during the subacute period after AMI and also improved these parameters at 6 months in the G-CSF group compared with the control group. Moreover, the G-CSF group showed better global and regional cardiac function than the control group during the subacute period as well as 6 months after AMI.

There have already been several investigations of early G-CSF treatment after PCI. When G-CSF therapy was commenced within 24 hours after PCI, Valgimihli et al. reported that LVEF showed a larger increase at 6 months and LVEDV was smaller in the G-CSF group compared with the placebo group (8). Ince et al. randomly assigned 25 of 50 patients to receive subcutaneous G-CSF (10µg/kg body weight) for 6 days from 89 ± 35 minutes after successful PCI. In the G-CSF group, the resting wall motion score index was significantly lower after 4 months compared with the control group. In addition, the wall motion score index following low-dose inotropic challenge was significantly lower in the G-CSF group than the control group after both 35 days and 4 months (3). Animal studies have demonstrated beneficial effects of G-CSF when treatment is initiated either before ischemic injury (9) or shortly after ischemic injury (10, 11), and early initiation of G-CSF has been shown to achieve better outcomes (12). Based on these results, early G-CSF therapy may improve LV function in patients with AMI. In the
FIRSTLINE-AMI trial (3), baseline cardiac function was evaluated just after PCI and showed no difference between the G-CSF and control groups. In our study, 123I-BMIPP SPECT was performed on day 6 after AMI, while myocardial perfusion and cardiac function were evaluated on day 9 by 99mTc-MIBI quantitative gated SPECT. Thus, the difference in the timing of evaluation between the two studies could be one reason for the different results obtained in the subacute period. There have also been reports about later initiation of G-CSF treatment after PCI, which have suggested that later initiation is not effective for improving LV function after AMI (13, 14). In the present study, we initiated G-CSF infusion at an earlier time after the onset of AMI than in other studies, so our findings suggest that the effectiveness of G-CSF may depend on the timing of treatment.

There have been several reports about the possible mechanisms by which G-CSF acts on the heart. Regeneration of myocardial tissue occurs after G-CSF administration due to a marked increase of circulating CD34-positive cells, which are precursors of various myocardial cells (15). In addition, the G-CSF receptor is expressed on cardiomyocytes and G-CSF activates the Jak/Stat pathway (12). G-CSF also blocks apoptosis of endothelial cells and promotes cardiac revascularization after myocardial infarction (12). However, recent

### Table 3 Myocardial Scintigraphies

| Variables | Control (n=20) | G-CSF (n=20) | p Value |
|-----------|---------------|--------------|---------|
| ES (MIBI) |               |              |         |
| Subacute  | 5.9 ± 3.6     | 4.3 ± 3.2    | 0.171   |
| 6 Months  | 5.2 ± 3.8*    | 2.8 ± 2.8#   | 0.024   |
| TDS (MIBI)|               |              |         |
| Subacute  | 15.6 ± 11.4   | 9.3 ± 9.1    | 0.063   |
| 6 Months  | 13.6 ± 11.8** | 5.9 ± 7.3#   | 0.02    |
| ES (BMIPP)|               |              |         |
| Subacute  | 6.7 ± 3.0     | 6.0 ± 3.1    | 0.309   |
| 6 Months  | 5.9 ± 2.8#    | 4.1 ± 2.8$   | 0.048   |
| TDS (BMIPP)|              |              |         |
| Subacute  | 22.2 ± 10.2   | 15.3 ± 10.5  | 0.079   |
| 6 Months  | 16.7 ± 9.9$   | 10.2 ± 8.9$  | 0.036   |

Severity of mismatched area

- BM-ES (sub) minus MIBI-ES (sub): 1.1 ± 2.7 vs. subacute: 1.6 ± 1.8, 0.496
- BM-ES (6Mo) minus MIBI-ES (6Mo): 0.7 ± 2.3 vs. subacute: 1.4 ± 1.4, 0.287
- BM-ES (sub) minus MIBI-ES (6Mo): 1.8 ± 2.8 vs. subacute: 3.2 ± 2.1, 0.076
- BM-TDS (sub) minus MIBI-TDS (sub): 5.7 ± 6.9 vs. subacute: 6.0 ± 6.3, 0.868
- BM-TDS (6Mo) minus MIBI-TDS (6Mo): 3.1 ± 5.6 vs. subacute: 4.3 ± 4.1, 0.427
- BM-TDS (sub) minus MIBI-TDS (6Mo): 7.6 ± 7.7 vs. subacute: 9.4 ± 7.0, 0.445

TDS: total defect score, ES: extent score, MIBI: 99mTc-sestamibi, BMIPP or BM: 123I-beta-methyl-p-iodophenylpentadecanoic acid, sub: subacute, 6Mo: 6 Months.

*: p<0.05 vs. subacute, **: p<0.01 vs. subacute, #: p<0.005 vs. subacute, $: p<0.0001 vs. subacute.

### Table 4 Functional QGS Parameters

| Variables        | Control (n=20) | G-CSF (n=20) | p Value |
|------------------|---------------|--------------|---------|
| LVEF (%)         |               |              |         |
| Subacute         | 46.6 ± 11.9   | 54.3 ± 10.7  | 0.039   |
| 6 Months         | 50.9 ± 11.4   | 59.0 ± 12.2* | 0.036   |
| EDV (ml)         |               |              |         |
| Subacute         | 127.1 ± 40.1  | 111.0 ± 32.1 | 0.168   |
| 6 Months         | 124.7 ± 40.1  | 108.5 ± 39.4 | 0.205   |
| ESV (ml)         |               |              |         |
| Subacute         | 67.5 ± 35.1   | 53.2 ± 27.0  | 0.157   |
| 6 Months         | 64.5 ± 35.5   | 48.2 ± 35.9  | 0.155   |
| PFR (EDV/sec)    |               |              |         |
| Subacute         | 1.79 ± 0.74   | 2.09 ± 0.88  | 0.262   |
| 6 Months         | 1.76 ± 0.46   | 1.95 ± 0.46  | 0.217   |
| RWMS             |               |              |         |
| Subacute         | 1.2 ± 1.3     | 2.1 ± 1.5    | <0.0001 |
| 6 Months         | 2.1 ± 1.6$    | 3.2 ± 1.3$   | <0.0001 |

LVEF: left ventricular ejection fraction, EDV: end-diastolic volume, ESV: end-systolic volume, RFR: peak filling rate, RWMS: regional wall motion score.

*: p<0.05 vs. subacute, $: p<0.0001 vs. subacute.
experimental studies have suggested that augmentation of cardiomyocyte regeneration in infarcted myocardium may be insufficient to explain the documented improvement of LV function by G-CSF (12, 15). It is possible that development of collateral circulation via vasculogenesis leads to improvement of myocardial ischemia (16) and it was reported that bone marrow cells mobilized by G-CSF differentiate to form vascular structures that could alleviate myocardial ischemia (2, 9). Thus, blocking apoptosis of endothelial cells and increasing myocardial revascularization after AMI could be important mechanisms by which G-CSF acts on the heart.

The present study showed that administration of G-CSF during PCI reduces infarct size and maintains LV function, suggesting that hyper early administration of G-CSF may suppress reperfusion injury, prevent expansion of the infarct zone, and preserve LV function.

We used a lower dose of G-CSF (2.0 μg/kg/day) than in other studies, which was selected because very-low-dose G-CSF (1.5 μg/kg/day) previously improved ischemia in patients with severe coronary artery disease (17).

**Limitations**

Several limitations of this study should be considered. First, we assessed the effectiveness of G-CSF for AMI in a relatively small number of subjects. Second, we performed semiquantitative evaluation of regional myocardial perfusion and regional function by using the same imaging modality. Third, myocardial fatty acid metabolism was also assessed by semiquantitative evaluation. If we had used positron emission tomography to evaluate absolute myocardial perfusion and myocardial fatty acid metabolism, we could have demonstrated the quantitative effects of G-CSF therapy. Accordingly, the long-term effects of G-CSF therapy should be investigated in a larger number of patients to confirm and extend our present findings.

**Conclusion**

Hyper early G-CSF therapy can improve myocardial perfusion, fatty acid metabolism, and cardiac function in AMI patients.

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