Use of granulocyte-colony stimulating factor during acute myocardial infarction to enhance bone marrow stem cell mobilization in humans: clinical and angiographic safety profile

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Aims There is increasing evidence that stem cell (SC) mobilization to the heart and their differentiation into cardiac cells is a naturally occurring process. We sought to assess the safety and feasibility of granulocyte-colony stimulating factor (G-CSF) administration in humans to enhance SC mobilization and left ventricle (LV) injury repair during myocardial infarction (MI).

Methods and results Twenty patients with STEMI (mean age, 61 ± 10 years), of whom 14 were submitted to primary percutaneous coronary intervention, were randomized to G-CSF (5 μg/kg/day s.c. for 4 consecutive days) or placebo. At entry and then at months 3 and 6, 99mTc-sestamibi gated-SPECT was performed to estimate extension of perfusion defect (PD) and LV function. The study drug was well tolerated and induced a significant increase of white blood count, CD34+ cells, and CD34+ cells coexpressing AC133 and VEGFR-2. At follow-up, treated and placebo groups did not differ for the angiographic coronary late loss and showed a similar pattern of PD recovery, whereas in the former at 6 months LVEF and especially LVEDV tended to be relatively higher (P = 0.068) and lower (P = 0.054), respectively.

Conclusion G-CSF administration in acute MI patients was feasible and did not lead to any clinical or angiographic adverse events and resulted in CD34+ and CD34+ AC133+ VEGFR2+ cell mobilization.

Introduction

There is increasing evidence that stem cell (SC) mobilization to the heart and their differentiation into myocytes and endothelial cells is a naturally occurring process.1,2 During acute myocardial infarction (MI), an increase of endothelial progenitor cells (EPC) and a selective homing of SC to the damaged heart have been described.3,4 Although the exact role of this potential self-repair mechanism is currently unknown, it has been hypothesized that manipulating its magnitude by cytokines administration soon after necrotic injury would boost LV recovery thereafter.

In mouse, cytokine-mediated bone marrow (BM) cell recruitment was beneficial in terms of improving heart function and survival during MI.5 However, in a primate model of acute MI, the combined use of SC factor (SCF) and granulocyte-colony stimulating factor (G-CSF) failed to improve myocardial function6 and in rats, the granulocyte-macrophage colony-stimulating factor (GM-CSF) induction by romurtide indeed facilitated infarct expansion and left ventricular (LV) remodelling.7 Therefore, the consequences of drug-induced EPC mobilization during MI are still unclear and possibly confounded by the effect of the pharmacological compound(s) employed for such an aim.8

The use of G-CSF during MI to recruit EPC and bone marrow SC has recently raised safety concerns because of an unexpected high restenosis rate in stented vessels.9 However, only three patients in the G-CSF group received angiographic follow-up, thus no clear conclusion about the incidence of restenosis can reasonably be drawn from this study.9
In an attempt to redefine its clinical-angiographic safety profile in this setting, we investigated the effect of G-CSF when given in humans soon after necrotic injury to improve LV recovery after the first MI.

**Methods**

**Study population**

Forty-seven patients, consecutively admitted for ST-segment elevation MI, were screened for possible inclusion. Sixteen of them were not eligible according to exclusion criteria and 11 refused to give informed consent. Therefore, 20 patients (16 men, 60 ± 11 years), randomized—with the use of computer based 1:1 randomization scheme—to either G-CSF (Filgrastim², Amgen kindly provided) (5 µg/kg/day s.c.) or placebo on a single blind basis for 4 consecutive days, constituted the study population of the present study. Exclusion criteria were previous MI, any haematological disorder, age <21 or >80, and Killip class >1. All patients received aspirin, β-blocker, statin, and angiotensin-converting enzyme inhibitor as standard therapy. According to protocol, the four patients in whom percutaneous coronary interventions (PCI) was not performed during hospitalization received coronary angiography before discharge.

Ethics Committee approval and written informed consent from all patients were obtained. Patients were asked daily to fill-in a form investigating the more common G-CSF side effects; self-reporting was also encouraged. Routine biochemical blood tests were performed according to protocols provided by manufacturers on a daily basis till 14 days after entry.

C-reactive protein was measured by nephelometry from fresh serum, according to the method of Behring Diagnostic. A criterion for G-CSF discontinuation was a white blood cells (WBC) count <5 000/mm³. For G-CSF discontinuation was achieved within the first 300 000/mm³ was performed on immunomagnetically purified peripheral blood CD34⁺ cells (Miltenyi Biotech) by triple labelling with peridinin chlorophyll protein-conjugated anti-CD34, PE-conjugated anti-CD133, unconjugated anti-VEGFR-2 followed by FITC conjugated swine anti-rabbit as secondary reagent.

**Statistical analysis**

The primary objective of the study was to evaluate the incidence of restenosis, angiographic follow-up procedure and at follow-up. All angiograms were evaluated according to the criteria used in the acute phase of MI. As this was a pilot investigation, no formal sample size was calculated. The second objective was evaluating the effect of G-CSF administration on LV improvement over time as assessed by ECG gated-SPECT.

Data are shown as mean ± SD or median and interquartile range where appropriate. Comparisons between two groups were performed with the Student’s t-test or Mann-Whitney U test, if variables were not normally distributed. Fisher’s exact test was used for categorical variables. Comparison among ECG-gated SPECT analyses performed at baseline and follow-up, among CD34⁺ cells evaluated at different time points in treated vs. placebo patients and among variables reported in Table 3 in treated vs. placebo patients was accomplished with ANOVA for repeated measures with a quadratic contrast for time and interaction between group and time, after having performed a Mauchly’s test of sphericity along with Greenhouse’s reduction of the degree of freedom where suitable. Post hoc comparisons for CD34⁺ cells evaluated at different time points were performed by Tukey’s honest significance test. Two-sided probability was significant at a level of <0.05. Statistical analyses were performed on Statistica 6.1 (Statsoft).

**Results**

The characteristics of the studied population are shown in Table 1. The two groups were well matched for age, sex, presentation profile, and treatment received.

Three patients in the treated and three in the placebo group were not submitted to primary PCI due to late presentation (51 ± 89 h); subsequently, one patient per group underwent elective PCI due to evidence of myocardial viability in the infarcted region. Overall, eight patients per groups were submitted to PCI with stenting immediately before or soon after G-CSF/placebo administration. Four patients per group received sirolimus eluting stent (SES). The angiographic profile of the patients is shown in Table 2. Cumulatively, time from symptoms onset to study drug administration was 37 ± 66 h (range 3–265), which reduced to 16 ± 19 (range 3–61) in those patients presenting within 12 h from symptoms.

G-CSF was well tolerated, with one patient presenting transient mild fever and two additional patients complaining headache after the first and third G-CSF injection, respectively. No bone or muscle discomfort was reported. The
safety WBC threshold was never reached, thus all randomized patients finally received the 4 day G-CSF regimen. WBC rose the day after the first treatment, peaking the morning after the last injection (35 ± 11 vs. 9 ± 2; P = 0.002) and returning to placebo values within 5 days. As a result of both total WBC count increase and a leftward shift of leucocyte formula, patients treated with G-CSF showed a marked elevation of both granulocytes and lymphocytes, but only a small non-significant increase of monocytes count (Table 3). No effect of study drug was recorded on erythrocytes and platelets count or on tested inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein (Table 3).

The active group presented a mild, transient but significant increase of alkaline phosphatase, and gamma-glutamyl transpeptidase (Table 3).

**CD34+ and EPC mobilization**

CD34+ mobilization is shown in Figure 1A. In G-CSF group, CD34+ cells peaked the day after the last G-CSF injection; at day 10 they still tended to be increased, being at day 14 back to placebo values. CD34+AC133+VEGFR2+ cells were increased in treated group both at days 4 and 10 (Figure 1B). In G-CSF-treated healthy subjects, the study drug resulted in a significant increase in both CD34+ (on average approximately seven-fold vs. baseline) and CD34+AC133+VEGFR2+ (>15-fold vs. baseline) (data not shown).

**Angiographic follow-up**

One patient in the placebo and none in the active group presented binary restenosis (Table 2). The late loss (in millimetres), expressed as median (interquartile range), was 0.3 (0.1–0.65) and 0.35 (0.05–0.55) in the treated and placebo group, respectively (P = 0.2).

**Effect of G-CSF on LV function and perfusion defect**

Perfusion defect (PD), expressed in SRS, and LV function evaluated in all 20 patients enrolled are shown in Figure 2. In both groups, SRS decreased and LVEF increased at months 3 and 6 compared with entry (Figure 2A, B, and C), whereas LVEDV tended to increase over time in a not significantly manner in both groups (Figure 2B).

No difference between treated and placebo group was observed in terms of SRS, LVEDV, and LVEF absolute values at follow-up (Figure 2A, B, and C, respectively); their relative changes over time are shown in Figure 2A’–C’. LVEF
and especially LVEDV per cent of increase tended to be, respectively, higher and lower in treated group at month 3 (15% ± 6 and 4% ± 4, respectively) and especially 6 (22% ± 10 and 6% ± 5) when compared with placebo patients (12% ± 5, \( P = 0.3 \); 7% ± 4, \( P = 0.09 \) and 14% ± 9, \( P = 0.074 \); 11% ± 5, \( P = 0.058 \)), respectively.

**Discussion**

The evidence that myocytes are not terminally differentiated in humans,2,14 coupled with the discovery that a variety of SC can indeed repopulate resident cardiac cells,1,4 such as endothelial cells or even cardiac muscle cells, is fostering an increasing interest in the field of SC biology. As preliminary evidence of benefit, it has been reported that circulating and resident BMSC or autologous skeletal myoblasts, when locally delivered into the heart, can ameliorate global or regional cardiac performance in different clinical scenarios.15–18 Moreover, the results of the BOOST trial suggest that, although of unclear extent yet, SC therapy, when delivered directly into the heart, is indeed beneficial.19 However, there are some concerns regarding the applicability of this approach in larger series of patients and so far, because of treatment complexity, this has been tested in few selected tertiary referral centers. The need to manipulate cells coupled with that to properly deliver them with high degree of precision in the cardiac tissue requires considerable resources investment, which implies that once/whether the treatment will be definitively proved to be beneficial, its cost effectiveness ratio should be also analysed in great detail before it can be recommend in the clinical arena.

During acute MI, an increase of EPC and a selective homing of SC to the damaged heart have been described.3,4 Although the exact role of this potential self-repair mechanism is currently unknown, it has been hypothesized that manipulating its magnitude by cytokines administration soon after necrotic injury would boost LV recovery thereafter.

Despite the fact that data reporting on its efficacy are pending, this treatment modality has raised considerable enthusiasm due to its potential widespread applicability. Moreover, the use of G-CSF to mobilize BMSC is safe, both at short- and long-term, thus prompting its use even in healthy volunteers as BM donors.20–23 However, G-CSF is known to exert a variety of pro-thrombotic effects acting on both coagulation proteins and platelets,24,25 thus its safety profile during or soon after an MI should be verified in phase I studies before its efficacy can be tested in larger number of patients.

Our results indicate that G-CSF administration during MI is indeed feasible. The study drug was well tolerated and did not lead to any clinical or angiographic adverse events. In particular, no thrombotic events occurred in treated patients despite systematic use of stents, both bare and sirolimus-eluting, during PCI. In addition, no binary restenosis occurred in the treated group and no difference in the late loss was observed compared with placebo patients. Consequently, our data do not support the recent findings, which led to premature study termination due to unexpected high restenosis rate in stented vessels by Kang et al.9 However, only three patients in the G-CSF and one in the placebo group received angiographic follow-up in the study, thus no conclusion about the real incidence of restenosis can be drawn.9 Nevertheless, several key differences among this study and ours should be cautiously noted. In the former, patients did not receive primary PCI as acute MI treatment and all patients presenting with in-stent restenosis were pre-treated with G-CSF for 4 days prior to vascular injury by PCI and stenting. G-CSF has the potential to activate neutrophils,24 for example, by stimulating adhesion to endothelial cells, thus influencing their recruitment at sites of inflammation and tissue injury (i.e. PCI) and possibly contributing to excess neointima proliferation and restenosis. Moreover, it should be underlined that in our series four patients in the treated group received drug eluting stent implantation during PCI and that the study drug regimen differed between the two studies. Further
Figure 2  Effect of G-CSF on infarct healing and LV function. In both groups, SRS decreased (A), LVEDV was unchanged (B), whereas LVEF (C) increased at follow-up. The relative change of SRS in respect to baseline at 3 and 6 months was similar in the two groups (A'), whereas LVEF (C') and especially LVEDV (B') per cent of increase tended to be, respectively, higher and lower in treated group at month 3 (15% ± 6 and 4% ± 4, respectively) and especially 6 (22% ± 10 and 6% ± 5) when compared with placebo patients (12% ± 5, P = 0.3; 7% ± 4, P = 0.09) and (14% ± 9, P = 0.074; 11% ± 5, P = 0.058), respectively.
### Table 3  Safety profile of G-CSF on circulating cells and biomarkers

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<th>Entry</th>
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<th>3(^{rd}) D</th>
<th>4(^{th}) D</th>
<th>5(^{th}) D</th>
<th>6(^{th}) D</th>
<th>10(^{th}) D</th>
<th>14(^{th}) D</th>
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<td><strong>WBC 10(^3)/mm(^3) (4–11)(^b)</strong></td>
<td>Placebo</td>
<td>12 ± 3</td>
<td>11 ± 3</td>
<td>13 ± 2</td>
<td>11 ± 3</td>
<td>9 ± 2</td>
<td>8 ± 3</td>
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<td></td>
<td>G-CSF(^a)</td>
<td>11 ± 3</td>
<td>26 ± 8</td>
<td>30 ± 8</td>
<td>32 ± 10</td>
<td>35 ± 11</td>
<td>24 ± 8</td>
<td>15 ± 9</td>
<td>10 ± 5</td>
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<td><strong>Neutrophils 10(^3)/mm(^3)</strong></td>
<td>Placebo</td>
<td>10 ± 3</td>
<td>8 ± 3</td>
<td>10 ± 2</td>
<td>9 ± 2</td>
<td>7 ± 3</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
<td>6 ± 3</td>
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<td></td>
<td>G-CSF(^a)</td>
<td>8 ± 3</td>
<td>23 ± 8</td>
<td>26 ± 8</td>
<td>27 ± 9</td>
<td>31 ± 10</td>
<td>19 ± 7</td>
<td>12 ± 9</td>
<td>8 ± 6</td>
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<td><strong>Lymphocytes 10(^3)/mm(^3)</strong></td>
<td>Placebo</td>
<td>1.3 ± 0.6</td>
<td>1.7 ± 0.3</td>
<td>1.9 ± 0.7</td>
<td>1.6 ± 0.3</td>
<td>1.8 ± 0.5</td>
<td>1.7 ± 0.4</td>
<td>2.2 ± 0.5</td>
<td>1.6 ± 0.6</td>
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<td>G-CSF(^a)</td>
<td>1.7 ± 0.4</td>
<td>1.7 ± 0.4</td>
<td>2.0 ± 0.6</td>
<td>2.3 ± 0.6</td>
<td>2.5 ± 0.6</td>
<td>2.1 ± 0.7</td>
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<td>2 ± 0.4</td>
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<td><strong>Monocytes 10(^3)/mm(^3)</strong></td>
<td>Placebo</td>
<td>0.5 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.1</td>
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<td>G-CSF</td>
<td>0.6 ± 0.2</td>
<td>0.9 ± 0.4</td>
<td>0.9 ± 0.3</td>
<td>1 ± 0.3</td>
<td>1.2 ± 0.4</td>
<td>1 ± 0.3</td>
<td>0.8 ± 0.4</td>
<td>0.3 ± 0.1</td>
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<td><strong>Hemoglobin g/dL (13–18)(^b)</strong></td>
<td>Placebo</td>
<td>13 ± 1</td>
<td>13 ± 0.5</td>
<td>13 ± 0.6</td>
<td>13 ± 0.6</td>
<td>12 ± 0.8</td>
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<td></td>
<td>G-CSF</td>
<td>13 ± 1</td>
<td>13 ± 1</td>
<td>12 ± 1.2</td>
<td>12 ± 1.4</td>
<td>12 ± 0.9</td>
<td>13 ± 1.1</td>
<td>12 ± 0.8</td>
<td>12 ± 0.6</td>
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<td><strong>Platelets 10(^3)/mm(^3) (150–450)(^b)</strong></td>
<td>Placebo</td>
<td>248 ± 101</td>
<td>229 ± 102</td>
<td>225 ± 91</td>
<td>199 ± 81</td>
<td>223 ± 89</td>
<td>252 ± 116</td>
<td>229 ± 85</td>
<td>262 ± 127</td>
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<td></td>
<td>G-CSF</td>
<td>231 ± 91</td>
<td>222 ± 87</td>
<td>214 ± 69</td>
<td>219 ± 86</td>
<td>222 ± 85</td>
<td>242 ± 68</td>
<td>206 ± 80</td>
<td>218 ± 96</td>
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<td><strong>Urate mg/dL (3.7–7.9)(^b)</strong></td>
<td>Placebo</td>
<td>5 ± 2</td>
<td>4.6 ± 1.2</td>
<td>4.7 ± 1.2</td>
<td>4.9 ± 1</td>
<td>5 ± 1</td>
<td>5.3 ± 1.9</td>
<td>5.5 ± 1.5</td>
<td>4.9 ± 1</td>
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<tr>
<td></td>
<td>G-CSF</td>
<td>5 ± 1</td>
<td>4.6 ± 1.6</td>
<td>4.8 ± 1.5</td>
<td>5 ± 1.3</td>
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<tr>
<td><strong>LDH IU/L (230–460)(^b)</strong></td>
<td>Placebo</td>
<td>618 ± 180</td>
<td>698 ± 202</td>
<td>1052 ± 207</td>
<td>898 ± 289</td>
<td>798 ± 301</td>
<td>687 ± 243</td>
<td>580 ± 201</td>
<td>598 ± 223</td>
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<td></td>
<td>G-CSF</td>
<td>704 ± 229</td>
<td>767 ± 208</td>
<td>970 ± 271</td>
<td>1079 ± 309</td>
<td>978 ± 204</td>
<td>698 ± 189</td>
<td>687 ± 253</td>
<td>587 ± 190</td>
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<td><strong>AP IU/L (104–296)(^b)</strong></td>
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<td>165 ± 45</td>
<td>156 ± 55</td>
<td>155 ± 54</td>
<td>151 ± 98</td>
<td>187 ± 23</td>
<td>166 ± 56</td>
<td>168 ± 65</td>
<td>155 ± 59</td>
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<td></td>
<td>G-CSF(^a)</td>
<td>155 ± 44</td>
<td>167 ± 38</td>
<td>196 ± 39</td>
<td>222 ± 44</td>
<td>255 ± 76</td>
<td>315 ± 116</td>
<td>269 ± 85</td>
<td>207 ± 65</td>
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<td><strong>γ-GT IU/L (5–60)(^b)</strong></td>
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<td>39 ± 18</td>
<td>38 ± 22</td>
<td>42 ± 25</td>
<td>41 ± 28</td>
<td>55 ± 39</td>
<td>65 ± 36</td>
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<td>47 ± 29</td>
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<td>122 ± 97</td>
<td>86 ± 67</td>
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<td><strong>ESR mm/h (0–29)(^b)</strong></td>
<td>Placebo</td>
<td>22 ± 14</td>
<td>19 ± 12</td>
<td>29 ± 18</td>
<td>34 ± 21</td>
<td>36 ± 19</td>
<td>24 ± 13</td>
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<td></td>
<td>G-CSF</td>
<td>31 ± 16</td>
<td>22 ± 11</td>
<td>29 ± 13</td>
<td>31 ± 18</td>
<td>39 ± 21</td>
<td>32 ± 11</td>
<td>29 ± 11</td>
<td>19 ± 8</td>
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<tr>
<td><strong>CRP mg/dL (0.0–0.8)(^b)</strong></td>
<td>Placebo</td>
<td>1.1 ± 0.9</td>
<td>1.9 ± 1.1</td>
<td>2.3 ± 1.4</td>
<td>2 ± 1</td>
<td>1.8 ± 0.9</td>
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<td>1.7 ± 1.2</td>
<td>0.8 ± 0.9</td>
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<td>G-CSF</td>
<td>0.9 ± 1</td>
<td>1.5 ± 1.1</td>
<td>1.1 ± 1.5</td>
<td>2.9 ± 1.8</td>
<td>2.6 ± 1.3</td>
<td>1.9 ± 1.2</td>
<td>1.6 ± 1.1</td>
<td>1 ± 0.7</td>
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\(\text{D: day; ESR, erythrocyte sedimentation rate; AP, alkaline phosphatase; γ-GT, gamma-glutamyl transpeptidase; CRP, C-reactive protein; LDH, lactate dehydrogenase.}
\[a\]P < 0.05 for the trend compared to placebo patients; \[b\]Range of normality provided by our laboratory; Arrows indicate time frame of G-CSF administration.
experiences are clearly needed to assess whether study drug dose has a role in explaining these different findings.

As expected, G-CSF led to an increase of AP and γ-GT, which was, as in healthy volunteers, transient and of limited magnitude. Noteworthy, no difference in the inflammatory profile was seen in treated vs. placebo patients.

G-CSF induced a significantly increase of CD34+ cells (on average greater than seven-fold vs. placebo group) and cells coexpressing CD34, AC133, and VEGFR2 (on average 16-fold vs. placebo group). Interestingly, the magnitude of G-CSF effect observed in healthy donors was mainly reproduced in AMI patients, suggesting that, at employed regimen, ongoing ischaemic myocardial necrosis does not affect G-CSF potency in mobilizing BM progenitor cells.

Our study was not aimed nor powered to assess the functional benefit of G-CSF administration in AMI patients. Accordingly, the effect of the study drug on LV function and recovery should be regarded as provisional and exploratory in nature.

No differences were noted in treated when compared with placebo patients in the absolute values of LV recovery parameters; however, in the former the relative increase of EF and EDV tended to be higher and lower, respectively. These findings should not discourage further studies in this setting, since acceleration of the healing process may be too low to explain cardiac function improvement.26 However, these findings should not discourage further studies in this setting, since acceleration of the healing process of the injured myocardium could play an important role for the beneficial effect of post-MI G-CSF treatment.27

Finally, the delay in administering G-CSF after symptoms onset could also be a critical issue: Orlic et al. 5 mobilized SC 5 days before experimental MI, whereas Norol et al. 6 recruited BM cells either before or immediately after coronary lesion. In our series, G-CSF was given 37 ± 66 h after symptoms onset: it is possible that at this later stage, mobilized SC are not as powerful as during earlier stages to regenerate the injured heart due to transient expression of signalling for SC-homing in the heart. 28

Conclusion

In conclusion, our study shows that G-CSF administration soon after MI in humans is feasible, well tolerated, with no evidence of cardiac adverse events, thus giving new inputs to determine the consistency of BMSC mobilization through G-CSF as a novel therapy for acute MI. The phase I exploratory nature of our investigation should not undergo under emphasized and further studies are needed to rule out the possibility of uncommon treatment-related side effects in this subset of patients.

References


