SCIENTIFIC LETTER

Safety of granulocyte-colony-stimulating factor in acute myocardial infarction (the Rigenera study)

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Intracoronary administration of bone marrow stem cells can improve left ventricular function after acute myocardial infarction (AMI)¹; however, it is invasive and therefore not widely applicable. Moreover, we have recently shown that the CD34 cell count is favourably correlated with left ventricular function changes after AMI.² Granulocyte-colony stimulating factor (G-CSF), a potent mobiliser of CD34 stem cells, might improve left ventricular function through their increased concentration.

Yet, a recent report raised concern about the safety of early G-CSF administration after AMI, followed by intracoronary cell injection and infarct-related artery (IRA) stenting, because of a strikingly high restenosis rate.³

The aim of our study was to assess the safety and the potential efficacy on cardiac function and perfusion of G-CSF administration in patients with a first large AMI.

METHODS

We enrolled eight patients with a first anterior AMI (all men, mean (standard deviation (SD)) age 54 (11) years, peak creatinine kinase 4615 (3998) U/l). Successful stenting of IRA within 7 days and left ventricular ejection fraction <45%. Exclusion criteria were cardiogenic shock, uncontrolled myocardial ischaemia or arrhythmias, malignancies, severe infections, haematological diseases, splenomegaly at abdominal echography and age >80 years. All patients were treated with lenograstim (recombinant human G-CSF) at a dose of 10 µg/kg/day for 5 days starting 5 days after coronary stenting. During hospitalisation and at 3 and 6 months, the occurrence of major adverse cardiac events (death, re-infarction and recurrence of angina) and myocardial function and perfusion by ^{99m}Tc-sestamibi gated-single photon emission computed tomography (SPECT) were assessed. End-diastolic and systolic volumes, left ventricular ejection fraction, summed motion score, summed thickening score and summed perfusion score were calculated using the Cedar's quantitative gated-SPECT programme. The extent of infarct area was computed as the percentage of left ventricle with severe perfusion, motion and thickening. Coronary angiography was repeated at 6 months. Coronary stenoses were measured by quantitative coronary angiography (Medis, the Netherlands). In-stent restenosis was defined as internal lumen reduction >50%. Late loss was calculated by the difference between the post-procedural minimal lumen diameter (MLD) and the MLD at the 6-month follow-up. The severity and extent of coronary disease were assessed according to Cianflone *et al.*⁴

Circulating CD34 cells and markers of thrombosis (platelet/monocyte aggregates and D-dimers) and inflammation (C reactive protein (CRP) and interleukin 6 (IL-6)) were assessed before and after G-CSF treatment and at follow-up. CD34 cells and platelet/monocyte aggregates were assessed by flow cytometry using antibodies anti-CD34 and anti-CD41a/CD14 (Caltag, Burlingame, California, USA), CRP by

immunonephelometry (Dade Behring, Marburg, Germany), and IL-6 and D-dimers by ELISA (R&D System, Oxford, UK; Asserachrom, Paris, France).

All patients were discharged on aspirin, clopidogrel, statins, angiotensin-converting enzyme inhibitors and β blockers. The study has been approved by the ethics committee of the Catholic University of Rome. All patients gave informed consent according to the Declaration of Helsinki.

Because of the sample size, non-parametric tests were used. Wilcoxon's and Mann–Whitney U tests were used as appropriate. Continuous variables were expressed as mean (SD); *p*<0.05 was considered significant.

RESULTS

All patients underwent a successful percutaneous coronary intervention (PCI) of the IRA (one primary, two rescue and five elective PCIs). Two patients exhibited critical stenoses in non-IRAs and were successfully treated with elective stenting. Overall, 12 bare metal stents were implanted. Post-procedural MLD was 2.72 (0.47) mm. No patient exhibited major adverse cardiac events or severe G-CSF-related side effects during hospitalisation and at follow-up. Two patients reported mild bone pain during G-CSF administration. All patients were asymptomatic at the 6-month follow-up.

The CD34 cell count significantly increased after G-CSF administration from 5.68 (3.47) to 45.46 (29.79) cells/µl (*p* = 0.004). D-dimers, platelet/monocyte aggregates and IL-6 values were similar at baseline and after G-CSF administration (*p* = 0.054, 0.38 and 0.063, respectively). Baseline CRP levels did not change after G-CSF administration (*p* = 0.063); levels at 3 and 6 months were significantly lower than those at baseline (*p*<0.001).

All parameters assessed by gated-SPECT scan were significantly better at 3 months than at baseline, and the improvement achieved significance for left ventricular ejection fraction, summed motion score, summed thickening score and summed perfusion score (*p* = 0.039, 0.0078, 0.0055 and 0.0025, respectively). Furthermore, infarct area decreased from 42.14% (9.51)% to 35.48% (7.97)% (*p* = 0.047). No further changes were observed at 6 months (table 1; fig 1).

At repeat angiography, mean (SD) late loss in the 12 stents implanted was 0.47 (0.59) mm; 2 of 8 (25%) patients exhibited in-stent restenosis successfully treated by drug-eluting stents. Only one patient showed a new critical stenosis in the right coronary artery, which was successfully treated by stent implantation. Notably, the extent of coronary

Abbreviations: AMI, acute myocardial infarction; CRP, C reactive protein; G-CSF, granulocyte-colony-stimulating factor; IRA, infarct-related artery; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; SPECT, single photon emission computed tomography

Figure 1 Baseline CRP levels. LVEF, left ventricular ejection fraction; SPS, summed perfusion score

disease assessed after PCI did not change at follow-up (mean (SD) extent score 7.29 (6.97) *v* 6.71 (5.02), extent index 0.32 (0.30) *v* 0.29 (0.22); *p* = 0.86). Nevertheless, lack of intravascular ultrasound assessment has to be acknowledged as a potential limitation of our study.

DISCUSSION

This present study shows that G-CSF is safe and potentially able to ameliorate left ventricular function and perfusion after AMI. Recently, safety concerns about G-CSF in post-infarction patients were raised by Kang *et al.*³ who reported 80% restenosis rate after G-CSF treatment. Instead, the restenosis rate in our study was 25%, with a late loss comparable with that found in previous trials on primary PCI (eg, 0.47 mm in this study *v* 0.82 mm in the controlled abciximab and device investigation to lower late-angioplasty complications (CADILLAC) trial),⁵ and in a very recent early

trial of G-CSF in AMI.⁶ Kang *et al.*³ however, performed IRA stenting (and intracoronary injection of peripheral mononuclear cells) after 4 days of G-CSF administration. Thus, the trauma of PCI took place under inflammatory conditions, potentially accounting for the high restenosis rate, which is known to be influenced by inflammation. Moreover, the safety of G-CSF in our study is corroborated by the fact that G-CSF did not result in detectable changes of thrombosis and inflammatory markers.

In our study, G-CSF was associated with a considerable improvement in left ventricular function and perfusion at follow-up, similar to that observed with intracoronary injection of stem cells in patients with AMI.¹ G-CSF utilisation might be particularly attractive for patients with AMI admitted to hospitals in which it is impossible to perform intracoronary stem cell injection, considering the favourable risk profile of G-CSF treatment. In a recent randomised trial, Valgimigli *et al.*⁷ failed to show a considerable beneficial effect of G-CSF on left ventricular function after AMI. However, the small number of patients, the broad inclusion criteria and the achievement of borderline significance limit the interpretation of these findings. Controlled randomised trials of the effect of G-CSF on left ventricular remodelling after AMI in a large population are warranted.

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Table 1 Biohumoral and gated-single photon emission computed tomography findings

	Baseline	Post-G-CSF	3 months	6 months
WBC (n/μl)	9157 (3983)	40 422 (11 465)†	8532 (2945)	6858 (763.48)
CD34 (n/μl)	5.68 (3.47)	45.46 (29.79)†	8.97 (7.94)	5.21 (3.3)
CD41α/14 (n/μl)	20.55 (30.60)	11.12 (14.16)	18.34 (19.25)	24.64 (21.86)
D-dimers (ng/ml)	500 (50)	416 (101)	—	—
CRP(mg/l)	31.30 (24.99)	20.04 (5.95)	0.663 (2.38)†	2.702 (2.55)†
IL-6 (ng/ml)	15.35 (16.98)	1.98 (3.44)	1.00 (2.22)	0 (0)
LVEDV (ml)	197 (52)	—	182 (56)	197 (51)
LVESV (ml)	139 (52)	—	118 (46)	128 (43)
LVEF (%)	31 (10)	—	37 (9)*	37 (8)
SMS	45 (12)	—	33 (12)†	30 (13)†
STS	32 (9)	—	20 (10)†	22 (9)*
SPS	30 (6)	—	17 (7)†	19 (7)†
Infarct area (%)	41.14 (9.51)	—	35.48 (7.97)*	36.76 (8.47)*

CRP, C reactive protein; G-CSF, granulocyte-colony-stimulating factor; IL, interleukin; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; SMS, summed motion score; STS, summed thickening score; SPS, summed perfusion score; WBC, white blood count.

**p* < 0.05 versus baseline; †*p* < 0.01 versus baseline.

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