Effectiveness and tolerability of administration of granulocyte colony-stimulating factor on left ventricular function in patients with myocardial infarction: a meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that granulocyte colony-stimulating factor was associated with small but significant improvements in left ventricular ejection fraction in patients with acute myocardial infarction at 3 to 12 months’ follow-up. The treatment was generally well tolerated in these patients. This was a generally well-conducted review, but the reliability of the authors' conclusions remains unclear given the differences between the studies.

Authors' objectives
To evaluate the effectiveness and tolerability of granulocyte colony-stimulating factor (G-CSF) on global left ventricular functioning in patients with myocardial infarction (MI).

Searching
MEDLINE, the Cochrane CENTRAL Register, EMBASE and the Science Citation Index were searched from inception to March 2007; the search terms were reported. Language restrictions were not imposed during the search, but only English language articles were eligible for inclusion in the meta-analysis. The reference lists of identified articles, published editorials and relevant reviews were checked.

Study selection
Randomised controlled trials (RCTs) of standard MI therapy comparing G-CSF treatment with placebo or blank control were eligible for inclusion. The dosage of G-CSF in the included studies ranged from 2.5 μg/kg for 5 days to 10 μg/kg for 7 days. In one study a cell infusion of monocytes 1 to 2 × 10^9 was also included in the treatment group. The mean time of initiation of G-CSF treatment ranged from 85 minutes to 7 days after MI for the acute MI group and 517 days for the old MI group. The control groups received placebo, saline or standard care. Studies of patients with a diagnosis of acute MI (≤14 days from the onset of new ST-segment elevation infarction) or old MI (>14 days since infarction) were eligible for inclusion. The mean age of patients in the included studies ranged from 49.8 to 63 years and the majority of patients were men. Studies of left ventricular ejection fraction (LVEF) and major adverse cardiovascular events (MACE) were eligible for inclusion. MACEs included ventricular arrhythmia, rehospitalisation for heart failure and a composite of other cardiovascular adverse events (cardiac death, recurrent MI, infarct vessel revascularisation procedure and stroke). In the included studies, LVEF was measured using echocardiography, quantitative left ventricular angiography, cardiac magnetic resonance imaging or ^99m{Tc}-sestamibi gated single-photon emission computed tomography. Minor adverse events were secondary outcomes; those reported in the included studies were bone pain, muscle discomfort, fatigue, mild fever, exanthema, nausea, headaches, dizziness, increase of creatine kinase and liver aminotransferase. Studies with a follow-up period of at least 3 months and no more than 12 months were eligible for inclusion. The included studies were carried out in Germany, Italy, China, Korea and Japan.

Two authors independently selected studies for inclusion.

Assessment of study quality
Study quality was assessed using the Jadad scale, which assesses randomisation, blinding, and the description of withdrawal and drop-outs. The maximum possible score was 5 points.

Two authors independently assessed the quality of the studies.

Data extraction
Where two studies using the same population were reported, data were extracted from the most recent study. The data extracted were the mean and standard deviation of baseline LVEF, LVEF at follow-up and the change in LVEF.
the mean change was not available, this was obtained by subtracting the baseline mean from the follow-up mean. The authors reported the equation used to calculate the standard deviation of the change in LVEF where this was not reported in the study. The numbers of major and minor adverse effects were extracted for each study.

It appears that two authors independently extracted the data.

**Methods of synthesis**

A meta-analysis was carried out using the pooled weighted mean difference (WMD) and a fixed-effect model. Where significant heterogeneity was detected, the analysis was repeated with a random-effects model. One trial was stratified into acute MI and old MI subgroups, one was stratified into 3- and 6-month follow-up subgroups, and one was stratified into 6- and 12-month follow-up subgroups. Heterogeneity was assessed using the Cochran Q test. Publication bias was assessed using the Begg rank correlation test and Egger's weighted regression test. A sensitivity analysis was carried out by excluding data from patients with old MI.

**Results of the review**

Seven RCTs (n=364) were included.

All studies scored 3 or more on the Jadad scale; two scored the maximum 5 points. Four studies were double-blind (n=208), two were single-blind (n=60) and one study did not specify blinding (n=96). There was no evidence of publication bias.

G-CSF was associated with a significant increase in LVEF at follow-up compared with the control group (WMD 2.96%, 95% confidence interval, CI: 0.98, 4.94, p=0.003); there was no evidence of heterogeneity. G-CSF was also associated with a significant increase in the change in LVEF compared with control groups (WMD 3.46%, 95% CI: 0.60, 6.32, p=0.018); there was evidence of significant heterogeneity (p=0.001), therefore a random-effects model was used. In the sensitivity analysis when the old MI subgroup was excluded, the difference between the G-CSF and control groups remained significant: LVEF at follow-up was 2.94% (95% CI: 0.89, 5.00, p=0.005) and change in LVEF was 3.85% (95% CI: 0.75, 6.96, p=0.015). G-CSF was not associated with a change in LVEF in patients with old MI (one study, mean change in LVEF was 0 in the treatment group and 0.2 in the control group).

The incidence of MACEs in the G-CSF group was 8.4%. The use of G-CSF was not associated with an increased risk of ventricular arrhythmia, rehospitalisation for heart failure, other cardiovascular events, or overall risk of MACEs. Other minor adverse events had low prevalence and were resolved spontaneously.

**Authors’ conclusions**

G-CSF was well tolerated in the populations studied and was associated with small but significant improvements in LVEF in patients with acute MI at 3 to 12 months’ follow-up.

**CRD commentary**

The review question was clear and the inclusion criteria were well-defined. Several relevant sources were searched. However, included studies were restricted to those reported in English, therefore it is not possible to rule out language bias. The authors did not seek unpublished material, but publication bias was assessed and ruled out. Appropriate steps were taken to minimise the possibility of reviewer bias or error in the study selection and validity assessment processes, and similar steps appear to have been taken at the data extraction stage. The authors used an accepted method to assess validity and the included studies were generally of a good quality. However, sample sizes were small and this might have resulted in insufficient power in the meta-analysis to detect differences between the groups. Statistical heterogeneity was assessed and accounted for in the analysis, and there was evidence of clinical heterogeneity between the included studies in terms of treatment regimen, time of initiation of the intervention and follow-up period. Therefore, the studies may have been better combined using a narrative analysis. Furthermore, the majority of patients included in the trials were men, so it is unclear to what extent the conclusions may be generalised to women. This was a generally well-conducted review, but the reliability of the authors’ conclusions is unclear given the differences between the studies.
Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that larger, longer term RCTs are needed.

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