Granulocyte colony-stimulating factor therapy for cardiac repair after acute myocardial infarction: a systematic review and meta-analysis of randomized controlled trials

Abdel-Latif A, Bolli R, Zubai-Surma EK, Tleyjeh IM, Hornung CA, Dawn B

CRD summary
This review concluded that granulocyte colony-stimulating factor therapy for cardiac repair in unselected patients with acute myocardial infarction appeared safe but did not provide an overall benefit. These conclusions reflected the evidence presented. However, small sample sizes of included studies and concerns in the review methods mean that a degree of caution might be required in interpreting these conclusions.

Authors' objectives
To assess the efficacy and safety of granulocyte colony-stimulating factor (G-CSF) therapy for cardiac repair in patients with acute myocardial infarction.

Searching
MEDLINE, EMBASE, CINAHL, Science Citation Index, The Cochrane Library and BIOSIS Previews and FDA were searched up to July 2007. Search terms were not reported.

Study selection
Randomised controlled trials (RCTs) that evaluated G-CSF therapy for cardiac repair in patients with acute myocardial infarction were eligible for inclusion. Studies that evaluated injected G-CSF-mobilised bone marrow cells by the intra-coronary route were excluded. The review efficacy outcomes included change in mean left ventricular ejection fraction, infarct scar size, left ventricular end-diastolic volume and left ventricular end-systolic volume. Safety outcomes were rates of death, recurrent myocardial infarction and in-stent restenosis.

Most of the included studies administered G-CSF 10µg/kg per day for five to six days; a few studies administered G-CSF 2.5µg/kg per day for five days. The time of initiation of G-CSF therapy ranged from 1.4 to 120 hours after acute myocardial infarction. The control arm of included studies was placebo. Peak white blood cell (WBC) count in included studies ranged from $29.4 \times 10^3$ to $55.0 \times 10^3$ WBCs/µL.

One reviewer assessed studies for inclusion.

Assessment of study quality
The quality of included studies was assessed with criteria of randomisation, concealment of allocation, baseline comparability, blinding, loss to follow-up and use of intention-to-treat analysis. Study quality was quantified using the five-point Jadad scale of randomisation, blinding and withdrawal.

Two reviewers independently performed the validity assessment.

Data extraction
For dichotomous outcomes, event rates were extracted to enable calculation of relative risks (RRs) with 95% confidence intervals (CIs). For continuous outcomes, mean and standard deviations were extracted to enable calculation of mean differences (MDs) with 95% CIs. Where data were available from more than one follow-up time points, the longest follow-up data were used in data analyses.

Two reviewers independently performed data extraction.

Methods of synthesis
Studies were combined in meta-analyses, using both fixed-effect models and random-effects models. Weighted mean
differences (WMDs) and pooled relative risks, with 95% CIs, were calculated. Statistical heterogeneity was assessed with the $I^2$ statistic. Publication bias was assessed with a funnel plot. Subgroup analyses were performed: mean left ventricular ejection fraction less than 50% at baseline versus mean left ventricular ejection fraction at least 50% at baseline; starting G-CSF therapy 37 hours or less after the acute event versus starting G-CSF therapy more than 37 hours; use of dose of G-CSF $\geq 10\mu g/kg$ per day versus use of the dose of G-CSF $< 10\mu g/kg$ per day; peak WBC count $42 \times 10^3$ WBCs/$\mu L$ or less versus peak WBC count more than $42 \times 10^3$ WBCs/$\mu L$; and peak CD34+ cell counts less than 37 cells/$\mu L$ versus peak CD34+ cell counts at least 37 cells/$\mu L$.

**Results of the review**

Eight RCTs were included in meta-analyses (n=385). Sample sizes ranged from 18 to 114. For study quality, concealment of allocation, baseline comparability and intention-to-treat analysis were adequate in all studies. Randomisation was adequately described in most studies. Four RCTs failed to blind participants and caregivers to study allocation; all studies had adequate blinding for outcome assessment. The loss to follow-up rate ranged from 0% to 16%. Duration of follow-up ranged from one to 12 months.

There were no significant differences between the G-CSF therapy and placebo group in terms of outcomes of left ventricular ejection fraction, infarct scar size, left ventricular end-diastolic volume and left ventricular end-systolic volume.

Subgroup analyses showed that G-CSF therapy was associated with a significant increase in left ventricular ejection fraction compared with placebo (WMD 4.73, 95% CI 2.67 to 6.79; seven RCTs) in studies with patients with mean ejection fraction less than 50% at baseline, but not in those studies with patients with mean ejection fraction at least 50% at baseline.

Subgroup analyses revealed a significant increase in ejection fraction when G-CSF therapy was initiated less than 37 hours after the acute event (WMD 4.65, 95% CI 2.51 to 6.80; five RCTs), but not when G-CSF therapy was initiated more than 37 hours after the acute event.

For the subgroup of patients with mean ejection fraction less than 50% at baseline, there were significant improvements in left ventricular end-diastolic volume (WMD -7.82, 95% CI -14.68 to -0.96) and left ventricular end-systolic volume (WMD -10.07, 95% CI -18.88 to -1.26). No significant results were found in other subgroup analyses.

There were no significant differences in rate of death, recurrent myocardial infarction and in-stent restenosis between the G-CSF therapy and placebo group either in the main analysis or in any subgroup.

A significant interaction was observed between the baseline left ventricular ejection fraction and the change in left ventricular ejection fraction ($p<0.0001$).

The authors stated that analyses using both fixed-effects and random-effects models yielded similar results for the major outcomes. Significant heterogeneity was observed only in the outcome of left ventricular ejection fraction when pooling all studies ($I^2=79.1\%$) and left ventricular ejection fraction for the subgroup of patients with mean ejection fraction less than 50% at baseline ($I^2=66.3\%$) and left ventricular ejection fraction for the subgroup of patients with initiation of G-CSF therapy less than 37 hours after the acute event ($I^2=75.2\%$).

The risk of publication bias was inconclusive based on the funnel plots.

**Authors' conclusions**

G-CSF therapy for cardiac repair in unselected patients with acute myocardial infarction appeared safe but did not provide an overall benefit. Subgroup analyses showed that G-CSF therapy may be beneficial in acute myocardial infarction patients with left ventricular dysfunction and when started early.

**CRD commentary**

This review's inclusion criteria were clear. A number of relevant databases were searched. The search for unpublished studies appeared to be limited, which increased potential for publication bias. The authors did not state whether language restrictions were applied in the search, which made it difficult to assess the risk of language bias. Only one
reviewer assessed studies for inclusion; therefore, reviewer error and bias could not be ruled out in the study selection process. Sufficient attempts were taken to minimise error and bias in data extraction and quality assessment. Relevant criteria were used to assess study quality. Statistical heterogeneity was assessed and appropriate methods were used to pool study results. Subgroup analyses were performed to assess the impact of a number of potential factors on the outcomes.

The authors' conclusions reflected the evidence presented. However, a degree of caution might be required in interpreting these conclusions, given the small sample sizes of included studies and concerns in the review methods.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that RCTs with a larger sample size were required to evaluate potential benefits of early G-CSF therapy in acute myocardial infarction patients with left ventricular dysfunction. Studies with longer follow-up periods were required to evaluate adverse events associated with G-CSF therapy.

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