Adjunctive granulocyte colony-stimulating factor therapy for diabetic foot infections

Reed K S, Pai M P

CRD summary
This review assessed the effects of adjunctive granulocyte colony-stimulating factors (G-CSF) for diabetic foot infections in non-neutropenic patients. The authors concluded that further research is required to assess the role of G-CSF in treating diabetic foot ulcers. The reliability of this conclusion is unclear given the limited search and unreported review methods.

Authors' objectives
To assess the effects of adjunctive granulocyte colony-stimulating factors (G-CSF) for diabetic foot infections in non-neutropenic patients.

Searching
MEDLINE was searched from inception to April 2004; the search terms were reported. In addition, the reference lists from relevant articles were checked.

Study selection
Study designs of evaluations included in the review
Inclusion criteria for the study design were not specified.

Specific interventions included in the review
Studies of G-CSF were eligible for inclusion. The included studies compared G-CSF plus standard care with standard care alone. The G-CSF used was filgrastim 5 microg/kg per day for 7 or 10 days or lenograstim 263 microg/day for 21 days. Standard care consisted of antibiotics with or without soft tissue and bone debridement and wound cleaning.

Participants included in the review
Studies of non-neutropenic patients with diabetic foot infections were eligible for inclusion. The included studies were conducted in patients with cellulitis, severe limb-threatening foot infections and pedal cellulitis or Wagner’s grade 2 foot lesion.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not specified. The included studies assessed a variety of outcomes: time to resolution of cellulitis, eradication of bacterial pathogens, intravenous antibiotic requirements, duration of hospital stay, clinical improvement, clinical response (time to resolution of infection and hospital discharge), amputations, need for surgical intervention and adverse effects.

How were decisions on the relevance of primary studies made?
The authors did not state how the studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity does not appear to have been formally assessed, although elements of methodological quality were noted in the individual descriptions of the primary studies.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
Methods of synthesis
How were the studies combined?
A narrative synthesis of the studies was undertaken.

How were differences between studies investigated?
Differences between the studies were discussed in the paper.

Results of the review
Three randomised controlled trials (RCTs; n=110) were included.

One double-blind RCT (40 patients with cellulitis) found that G-CSF (filgrastim) significantly reduced hospital stay (median 10 versus 17.5 days), and speeded up resolution of cellulitis (median 7 versus 20 days), duration of intravenous antibiotics (median 8.5 versus 14.5 days) and time to negative cultures (median 4 versus 8 days) (P<0.05 for all outcomes). The RCT found transient bone pain not requiring treatment in 3 patients receiving G-CSF.

One RCT with blinded outcome assessment (40 patients with severe limb-threatening foot infection) found no statistically significant difference between G-CSF (lenograstim) and control in clinical improvement rates at 3 weeks (60% versus 45%, P=0.34), but found significantly fewer amputations at 9 weeks with G-CSF (3 versus 9, P=0.038). No adverse effects of G-CSF were found.

The third RCT (30 patients with pedal cellulitis or Wagner's grade 2 foot lesions) found no statistically significant difference between G-CSF (filgrastim) and control in clinical response, duration of hospital stay (27 versus 28 days), duration of antibiotics, or amputation rates (13.5% versus 20%, P>0.05). The RCT found significantly higher neutrophile counts at 5 and 10 days with G-CSF (P=0.001) and increased phagocytic ability of neutrophils (P=0.004). No adverse effects of G-CSF were found.

Authors' conclusions
Further research is required to assess the role of adjunctive G-CSF in treating diabetic foot ulcers.

CRD commentary
The review question was clear in terms of the intervention and participants, whereas inclusion criteria for the study design and outcomes were not specified. Limiting the search to one electronic database and reference lists might have resulted in the omission of other relevant studies. No attempt was made to locate unpublished studies, thus raising the possibility of publication bias. In addition, it was unclear whether any language restrictions had been applied. The methods used to select studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce errors and bias. Validity was not formally assessed although some aspects of validity were discussed in the paper. A narrative synthesis was appropriate given the clinical heterogeneity between studies. Although the authors' conclusion appears to follow from the results presented, their limited search strategy and poor reporting of the review process make it difficult to confidently assess the reliability of the review.

Implications of the review for practice and research
Practice: The authors stated that further research is required before G-CSF should be used clinically.

Research: The authors stated that a larger double-blind RCT is required to assess the effects of G-CSF plus a standard antimicrobial regimen, and to determine the optimal dose, duration and type of G-CSF and the patient subgroups that may benefit most from adjunctive G-CSF.

Bibliographic details
Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Infective Agents /therapeutic use; Diabetic Foot /drug therapy; Drug Therapy, Combination; Granulocyte Colony-Stimulating Factor /therapeutic use; Hematinics /therapeutic use; Humans; Randomized Controlled Trials as Topic; Treatment Outcome

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.