Safety of GM-CSF in patients with AIDS: a review of the literature
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Authors' objectives
To undertake a systematic review of all clinical studies reporting outcomes in patients with the acquired immunodeficiency syndrome (AIDS) receiving granulocyte-macrophage colony-stimulating factor (GM-CSF) for any indication.

Searching
MEDLARS was searched from 1966-1996 using the terms AIDS, HIV, granulocyte-macrophage colony-stimulating factor, GM-CSF and sargramostim. AIDSline Internet sites, and Current Contents were also searched (weekly), as were bibliographies of retrieved clinical trials and review articles.

Study selection
Study designs of evaluations included in the review
Clinical studies, case series and case reports. Two of the included studies were RCTs, 3 were non-randomised trials, 2 single case reports and 15 case series. Study duration ranged from 8 days to 6 months.

Specific interventions included in the review
Granulocyte-macrophage colony-stimulating factor (GM-CSF) versus control (no intervention). Wide ranges of fixed and variable dosages were reported across the studies. Two studies reported intravenous administration, and the rest used subcutaneous administration apart from one which administered it intralesionally. Some studies required patients to begin or continue with concurrent antiretroviral therapy (zidovudine).

Participants included in the review
Patients with the acquired immunodeficiency syndrome (AIDS) or HIV infection receiving granulocyte-macrophage colony-stimulating factor (GM-CSF) for any indication. The majority of participants in the studies were adult males, with only one study of children. Thirty eight percent of the participants had an AIDS related cancer (Kaposi's sarcoma and non-Hodgkin's lymphoma). Forty six percent had neutropenia that was attributed to zidovudine or to AIDS in general. The remaining 16% had specific infections such as cytomegalovirus retinitis and bacteremia.

Outcomes assessed in the review
Key outcomes were basic and specialised tests of immune capabilities; major clinical events such as new infections, new neoplasms or progression of existing cancers; haematological and non-haematological toxicities such as myalgias and fevers; and measures of HIV replication and cultures.

How were decisions on the relevance of primary studies made?
Titles and abstracts were reviewed to determine whether they met the inclusion criteria. One research analyst, one research assistant and a physician reviewer screened all abstracts and papers for eligibility. Differences were resolved by referring back to the full study report.

Assessment of study quality
Randomised studies were scored for methodological quality using the Jadad scale (see Other Publications of Related Interest no.1). Quality scores served as a measure of the internal validity of the randomised studies. Data on quality were extracted by two reviewers at the same time as other data were extracted.

Data extraction
All studies were extracted using data extraction forms developed for the project. Data were extracted by the physician reviewer with a research assistant performing duplicate extraction. Differences were resolved through discussion and by
referring to the original papers. Data were collected on study descriptors, patient descriptors, and treatment descriptors.

**Methods of synthesis**
How were the studies combined?
Narrative summary as meta-analysis was deemed inappropriate for this data set.

How were differences between studies investigated?
The results of RCTs were reported separately from the results of other study designs in tables but not in the text.

**Results of the review**
Twenty-two studies with a total of 274 patients: 12 addressed AIDS neutropenia, 8 AIDS cancer therapy, and 2 opportunistic infections.

Safety outcomes included human immunodeficiency virus replication, immune status, and frequency of opportunistic infections and neoplasms. Viral burden was assessed by serum p24Ag in 15 studies. Nine reported no change in levels, three net decreases, and three net increases. All studies showing net increases involved patients receiving GM-CSF without a concurrent antiretroviral. The CD4 counts were unchanged in 5 studies, increased in 3, and not reported in 14. The incidence of neoplasms or new opportunistic infections was low.

**Authors’ conclusions**
Clinical trials to date do not provide conclusive evidence regarding the safety of GM-CSF in HIV-infected patients covered by concurrent zidovudine, although they send no clear or consistent signal of increased risk at this time.

**CRD commentary**
This is a well-conducted systematic review. Inclusion criteria are clearly stated. Methodological aspects of the review such as data extraction and assessment of validity are clearly described. The authors discuss the deficiencies of the quantity and quality of the data. However, study results were not clearly reported, and results were discussed narratively for both RCTs and other study designs together. Furthermore, one of the authors worked at Immunex Corporation who also funded the review and produce GM-CSF. Given the limitations of the data included in the review, the author’s conclusions could have been more cautious.

**Implications of the review for practice and research**
The authors state that only clinical trials will provide the necessary information to complete our understanding of the effects of GM-CSF in HIV-infected patients.

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**Other publications of related interest**
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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.