Granulocyte macrophage colony-stimulating factor as an adjuvant for hepatitis B vaccination: a meta-analysis
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CRD summary
This review concluded that adjuvant granulocyte macrophage colony-stimulating factor is associated with a dose-dependent increase in response rate to the hepatitis B virus vaccine in both healthy individuals and patients with renal failure. The conclusions reflect the review findings. However, limited reporting of the review methods and the potential effects of poor-quality studies make it difficult to confirm the reliability of the results.

Authors' objectives
To assess the efficacy of granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance the immune response to the hepatitis B virus (HBV) vaccine.

Searching
MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews were searched up to March 2005; the search terms were provided. In addition, the bibliographies of retrieved articles were checked.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of HBV vaccine with adjuvant GM-CSF compared with HBV vaccine alone or placebo were eligible for inclusion. The majority of the included studies assessed between one and four primary doses of HBV vaccine, but 3 studies assessed booster doses of vaccine. The doses of GM-CSF ranged from 20 to 300 microg, and were administered either subcutaneously or intramuscularly.

Participants included in the review
The authors did not specify what types of participants were eligible for inclusion. The majority of the included studies assessed healthy participants; two studies involved participants with chronic renal failure and haemodialysis, while a further study involved participants infected with the human immunodeficiency virus. Most participants were receiving primary HBV vaccination; however, three studies used participants who were nonresponders.

Outcomes assessed in the review
The primary outcome was rate of response to HBV vaccine after the first and final vaccine doses. Other eligible outcomes included anti-HBs antibody titres, side-effects and haematological profile.

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

Assessment of study quality
Two reviewers independently assessed the studies for validity, with any disagreements arbitrated by a third reviewer. Validity was assessed using the Jadad scale, based on the following criteria: method of randomisation, double-blinding, and reports of drop-outs and withdrawals.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The rate of response to the HBV vaccine (ant-HB > 10 UI/L) was extracted, and rate ratios (RRs) with 95% confidence intervals (CIs) were calculated. Where available, anti-HBs antibody titres were extracted and mean differences with standard deviations were calculated.

**Methods of synthesis**

How were the studies combined?
The pooled RR and 95% CI were calculated using a fixed-effect meta-analysis unless statistical heterogeneity was observed, in which case a random-effects model (DerSimonian and Laird) was used. The Woolf method was used to calculate 95% CIs. Pooled standard mean differences (SMDs) with 95% CIs were calculated for antibody titres. Other outcomes were discussed in a narrative. Publication bias was assessed using funnel plots, the rank correlation test and the regression asymmetry test.

How were differences between studies investigated?
Heterogeneity was assessed using Cochran's Q test and the I-squared test. Heterogeneity was deemed significant when the p-value was less than 0.1. A sensitivity analysis was performed to determine the effect of excluding individual studies. Random-effects meta-regression and logistic regression were also used to explore heterogeneity between the studies.

**Results of the review**

Thirteen RCTs (n=734) were included in the review.

Quality: the median Jadad quality score was 2 (range: 1 to 5). Only four studies described an appropriate method of randomisation; three studies were defined as double-blind; only one study, which was defined as single blind, adequately reported the method of concealment.

Antibody response: the response to the HBV vaccine was significantly better in participants who received GM-CSF adjuvant to HBV vaccine than in those who did not also receive GM-CSF, both after the first dose (RR 1.54, 95% CI: 1.04, 2.27; p=0.03; 10 studies) and after the final dose (RR 1.20, 95% CI: 1.02, 1.41; p=0.023; 9 studies), using the random-effects model.

Anti-HBs antibody titres: participants with renal failure who received GM-CSF adjuvant to HBV vaccine had significantly higher anti-HBs antibody titres than in those who did not also receive GM-CSF (SMD 1.84, 95% CIs 0.97, 2.71; p<0001; 4 studies), using the random-effects model.

Other outcomes: no significant serious adverse events appeared to be associated with GM-CSF. Where effects were reported they were mainly mild (injection site-related, headaches, nausea, fever and fatigue). No clinically significant haematological differences were observed.

Heterogeneity: removing single studies from the analysis resulted in only minimal changes in effect size. The logistic model identified a significant positive relationship between antibody response rate and dosage of GM-CSF and confirmed the presence of between-study heterogeneity.

Publication bias: no evidence of significant publication bias was found.

**Authors' conclusions**

GM-CSF significantly increased the response rate to the HBV vaccine in both healthy individuals and renal failure patients, with higher doses of GM-CSF increasing the probability of response to the HBV vaccine. GM-CSF given as an adjuvant to HBV vaccination also increased anti-HBs antibody titres in renal patients.
CRD commentary
The review question was clear in terms of the study design, interventions and outcomes of interest; the participants of interest were not specified. The authors carried out a reasonable search for relevant studies but made little attempt to identify unpublished studies. Although the authors reported that no evidence of publication bias was apparent from statistical tests, the power of these tests was unclear given the relatively small number of studies included in the review. The potential for language bias was also unclear, although no language restrictions were reported. Similarly, it was unclear whether appropriate attempts were made to reduce the potential for reviewer bias and error when selecting studies and extracting the data. The authors did, however, try to reduce the risk of bias when assessing the quality of the included studies. The criteria used to assess quality were appropriate and the results were summarised. However, the individual quality scores were not reported and the median quality score suggested that the overall quality of the studies was only average; the individual scores appeared to range from poor to good. The impact of study quality on the results was also not investigated.

The review included adequate details about the included studies. The statistical synthesis seems appropriate. The authors assessed statistical heterogeneity and analyses were performed to investigate potential sources of heterogeneity between the studies. Overall, the authors’ conclusions appear to follow from the results. However, poor reporting of the review methods and the potential effects of poor-quality studies make it difficult to assess the reliability of the findings.

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

Research: Further well-designed studies, with an appropriate follow-up, are needed to establish the optimal dose, the number of GM-CSF injections, the cost-effectiveness of the intervention, and the duration of protective antibody levels over time.

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