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Granulocyte macrophage colony-stimulating factor as an adjuvant for hepatitis B vaccination: A meta-analysis

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Abstract

The efficacy of granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance the immune response to hepatitis B virus vaccine has been object of several reports. We searched for randomized controlled clinical trials comparing GM-CSF given concomitantly to hepatitis B virus vaccine to vaccine given alone or with placebo. Data on rates of seroconversion (anti-HBs titers >10 IU/ml) from 13 studies (734 subjects) produced combined estimates that favored GM-CSF as compared to controls: rate ratio after a single immunization was 1.54 [95% confidence interval (CI), 1.04–2.27] and 1.20 (95% CI, 1.02–1.42) at the end of the vaccination cycle. Using a logistic approach a significant dose/response effect of GM-CSF was seen. Moreover, in renal failure patients who have responded to the vaccine, GM-CSF increased anti-HBs titers. Our findings suggest that GM-CSF induced a significant effect in terms of response rate and achievement of an earlier seroconversion to the vaccine in the overall populations examined, in renal failure patients and in healthy individuals.

Keywords: Granulocyte macrophage colony-stimulating factor; Hepatitis B vaccine; Meta-analysis

1. Introduction

Immunization is the most effective way to prevent transmission of hepatitis B virus (HBV) and, hence, the development of acute or chronic hepatitis B. Seroprotection after recommended schedule and routes of immunization is achieved in 90–99% of immunocompetent individuals, but hyporesponsiveness to HBV vaccine is well recognized in immunocompromised people [1–3]. Predictors of non-response include increasing age, male gender, obesity, tobacco smoking, alcoholism and immunocompromising chronic disease [4–8]. Actually, the antibody response is lower in patients with diabetes mellitus, renal failure and chronic liver disease, as well as in immunocompromised patients, such as those infected with HIV.

Strategies to improve the HBV vaccine response rate have included the use of higher vaccine dose or increasing number of doses, use of different route of administration (e.g., intradermal versus intramuscular administration), accelerating dosing schedule and use of adjuvants such as antigen delivery systems and various immunomodulators [3,9–17].

There is growing evidence that granulocyte macrophage colony-stimulating factor (GM-CSF) enhances the immune response to vaccines direct against both infectious agents and various cancers [16,17]. GM-CSF has a variety of effects on immune responses and coimmunization with GM-CSF has been shown to increase the antibody response and to enhance the proliferative response of T cells [18,19]. The efficacy of GM-CSF as adjuvant to hepatitis B vaccine has been object of several clinical trials conducted in healthy subjects, patients with end-stage renal disease and HIV-infected patients [20–44].

This study aims to systemically identify and summarize the quality of the controlled trials available and the effects

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GM-CSF as adjuvant to HBV vaccine (part of this study was presented at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, December 16–19, 2005).

2. Materials and methods

2.1. Search strategies

The search was carried out on MEDLINE (1966–March 2005), EMBASE (1980–March 2005), The Cochrane Database of Systematic Reviews (Issue 1, 2005). MeSH terms used were "Granulocyte macrophage colony-stimulating factor", "vaccines", "hepatitis B vaccine", "adjuvants, immunologic". The syntax used for the MEDLINE searches was: granulocyte macrophage colony-stimulating factor AND vaccines; granulocyte macrophage colony-stimulating factor AND HBV vaccines; adjuvant, immunologic AND HBV vaccine. The computer search was supplemented by consulting the bibliographies from the articles retrieved.

2.2. Selection criteria and outcome measures

We included randomized controlled clinical trials comparing the efficacy of hepatitis B vaccine given with or without GM-CSF as vaccine adjuvant. Data on rate of response to HBV vaccine (anti-HBs >10 UI/l) in patients receiving GM-CSF and controls were extracted. The meta-analytical pooling was performed at two time-points: after the first and the last (third or fourth) vaccine dose during the immunization cycle. We also extracted data, where possible, on anti-HBs antibody titres, side effects and on hematological profile.

2.3. Quality assessment

We assessed the methodology of each trial with a scale developed by Jadad et al. that scores (from a low of 0 to a high of 5) the randomization, double blinding and reports of dropouts and withdrawals [45]. Each trial was independently scored by two of us and any areas of disagreement arbitrated by a third.

2.4. Statistical analysis

A conventional meta-analysis was performed with use of the Mantel–Haenszel fixed-effects model and applying the DerSimonian and Laird random effects model in cases where the heterogeneity test give a p value <0.1 [46,47]. We calculated both the study-specific and the common, 95% confidence intervals (CIs) by the method of Woolf [48]. We used rate ratio (RR) as measure of the effect size, and the procedure to combine the 2×2 tables was the Mantel–Haenszel like method by Greenland and Robins [49,50].

Differences in anti-HBs antibody titers among GM-CSF recipients and controls were evaluated by the standardized mean difference, which is the difference in means divided by a standard deviation [50,51].

Sensitivity analysis was performed for determining if quantitative results differed with the exclusion of individual studies. We used random effect meta-regression to explore the influence of possible sources of heterogeneity on treatment effect. This was done according to the study population (healthy subjects versus dialysis patients) and the number of GM-CSF doses (single dose versus multiple doses). The meta-regression was done by regressing the study-level RR (dependent variable) against a study-level covariate treated as a dicotomic variable.

Finally, the influence of four explanatory (independent) variables [GM-CSF dose, primary vaccination procedure versus booster in non-responders, HBV vaccine schedule (number of administered doses), and renal failure] was evaluated employing a maximum likelihood approach. GM-CSF dosage and HBV vaccine schedule were quantitative, whereas primary vaccination and renal failure were binary (yes/no) variables. Since the outcome was a binomial variable (successful immunization: yes/no), a random effects logistic regression analysis was done. The heterogeneity of the data was addressed by stratifying for the different studies. The software package Stata 9.1 was used for this task.

2.5. Assessment of publication bias and heterogeneity

Graphical funnel plots were generated to visually inspect for publication bias [52]. The statistical methods for detecting funnel plot asymmetry were the rank correlation tests of Begg and Mazumdar and the regression asymmetry test of Egger et al. [52,53].

The heterogeneity of study results was assessed by the Cochran's Q and by a test of inconsistency (I^2) [54,55].

3. Results

As shown in the flow diagram (Fig. 1), 31 potentially relevant clinical trials were identified and retrieved for more detailed evaluation. Of these, six studies were excluded because reported data not relevant to study question. We also excluded six uncontrolled clinical trials evaluating GM-CSF as an adjuvant for hepatitis B vaccination [20–22,24,38,44], and five studies controlled but not randomized [25,27,32,35,37]. One report [34] was identified as duplicate publications and was considered under their primary reference [42] Therefore, we included in the meta-analysis data retrieved from 13 randomized clinical trials for a total of 734 patients [23,25–31,33,39–43].

3.1. Description of studies and quality assessment

Table 1 summarizes the main characteristics of included studies. Data were published as full-length paper or, in two cases, as abstract. Seven studies were conducted in patients