Effects of oral levamisole as an adjuvant to hepatitis B vaccine in adults with end-stage renal disease: a meta-analysis of controlled clinical trials

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CRD summary
The authors concluded that the results suggested significantly increased seroprotection with levamisole given with hepatitis B virus vaccine in patients with end-stage kidney disease. The authors' conclusions appeared to reflect the evidence, but limitations in the search and trial quality assessment, plus findings based on a small number of included trials of diverse design, means that their reliability is unclear.

Authors' objectives
To evaluate the efficacy and safety of oral levamisole (immune modulator) as an adjuvant to hepatitis B virus vaccine in patients with end-stage renal disease.

Searching
MEDLINE, SCOPUS, Science Citation Index and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for studies published in English in peer-reviewed journals between 2000 and 2009. Search terms were reported.

Study selection
Prospective controlled trials that compared levamisole plus hepatitis B virus vaccine versus hepatitis B virus vaccine alone were eligible if they were in patients undergoing dialysis and/or patients with chronic renal disease not yet requiring dialysis. Trials could use any dosing regime or administration route of recombinant DNA or plasma-derived hepatitis B virus vaccine; trials could include patients with previous hepatitis B virus vaccination. Eligible trials had to report adequate measures of response rate at completion and six to 10 months after completion of the hepatitis B virus vaccination schedule. Response rate was defined as the proportion of patients achieving seroprotection (hepatitis B virus surface antigen concentration above 10mIU/ml). Trials were excluded if they were in patients with: positive serology for hepatitis B virus surface antigen (HBsAg); antibodies to HBsAg, antibodies to hepatitis B virus core antigen or HIV; or in receipt of concurrent immunosuppressive agents.

The primary review outcome was response rate. The other outcome assessed was tolerability (i.e. dose reduction, levamisole discontinuation, and adverse events including laboratory abnormalities).

All but one of the included trials evaluated adjunctive oral levamisole (80 to 120mg) after each haemodialysis session for four to six months; the other study evaluated oral levamisole 100mg/day for six days before and six days after each hepatitis B virus vaccination. All of the included trials used recombinant hepatitis B virus vaccine. All patients were on standard haemodialysis. The mean age of included patients ranged from 41 to 53 years; the percentage of men ranged from 53 to 68%; the mean duration of dialysis ranged from 12 to 51 months. Trials included vaccination-naive patients and patients who had not responded to previous hepatitis B virus vaccination.

Two reviewers selected studies and agreed on the selection.

Assessment of study quality
Validity was apparently assessed using randomisation and blinding.

The authors did not state how many reviewers assessed validity.

Data extraction
Data on rates of seroconversion six to ten months after completion of vaccination schedule were extracted from patients who completed the vaccination schedule (per protocol analysis).
Data were extracted onto a spreadsheet by one reviewer and rechecked twice.

**Methods of synthesis**

Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated using a Mantel-Haenszel fixed-effect method. Heterogeneity was assessed using the $X^2$ and $I^2$ statistics. Analyses appeared to be repeated using a random-effects model.

Randomised controlled trials (RCTs) in vaccination-naive patients were analysed separately.

The possibility of publication bias was assessed using Begg and Mazumdar and Egger's tests.

**Results of the review**

Four trials were included in the review (n=328 patients). The authors stated in the text that three trials used a randomised design, but that one of these selected patients randomly; in the tables, the authors classified three trials as randomised controlled trials (RCTs, n=284 patients) and one as a non randomised controlled trial (n=44 patients). One of the RCTs was double-blinded and used apparently adequate randomisation methods.

**Efficacy:** Adjuvant oral levamisole was associated with a statistically significant increase in response rate after completion of the hepatitis B virus vaccination schedule (OR 2.77, 95% CI 1.56 to 4.94) and six to 10 months after completion of hepatitis B virus vaccination schedule (OR 3.96, 95% CI 1.71 to 9.18). No significant heterogeneity was found for either analysis. Results were similar for trials of vaccine-naive patients.

**Tolerability:** Five patients underwent dose reduction due to mild adverse events. One trial reported three deaths (one in the levamisole group). No other serious adverse events were reported.

There was no evidence of publication bias.

**Authors’ conclusions**

Results suggested significant benefits in increased seroprotection with levamisole as an adjunct to hepatitis B virus vaccine in patients with end-stage renal disease.

**CRD commentary**

The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched, but no attempts were made to minimise publication or language bias, so some other relevant studies may have been missed. No evidence for publication bias was found, but the assessment was of limited value given the small number of included trials. Methods were used to minimise reviewer errors and bias in the selection of studies and the extraction of data.

The assessment of study quality was limited. There appeared to be some confusion over the classification of one trial (that randomly selected patients) as an RCT. The limited assessment of quality made it difficult to judge the reliability of included trials and review findings. Heterogeneity was assessed. For the main analysis, data from trials of diverse design were pooled; this may not have been appropriate.

The authors’ conclusions appeared to reflect the evidence, but the relatively limited search and assessment of trial quality, plus findings based on a small number of included trials of diverse design, means that their reliability is unclear.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that large RCTs of oral levamisole as an adjunct to hepatitis B virus vaccine, with longer follow-up, are required to confirm the findings of this review.
Funding
Not stated.

Bibliographic details

PubMedID
20171406

DOI
10.1016/j.clinthera.2010.01.005

Original Paper URL
http://www.clinicaltherapeutics.com/article/S0149-2918(10)00006-8/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Adjuvants, Immunologic /administration & dosage /pharmacology; Administration, Oral; Controlled Clinical Trials as Topic; Drug Therapy, Combination; Hepatitis B /immunology /prevention & control; Hepatitis B Antibodies /drug effects /immunology; Hepatitis B Vaccines /therapeutic use; Humans; Kidney Failure, Chronic /immunology /therapy; Levamisole /administration & dosage /pharmacology; Prospective Studies; Renal Dialysis /adverse effects

AccessionNumber
12010002555

Date bibliographic record published
04/08/2010

Date abstract record published
25/05/2011

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.