Meta-analysis: the adjuvant role of thymopentin on immunological response to hepatitis B virus vaccine in end-stage renal disease

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CRD summary
The review assessed whether thymopentin improved the response to hepatitis B vaccination in patients on dialysis who had end-stage renal disease. The authors concluded that only patients treated with higher doses showed significant improvement. The quality of the evidence and the analysis presented in this review was questionable. Better research is needed to confirm the conclusions.

Authors' objectives
To evaluate the efficacy and safety of thymopentin as an adjuvant to hepatitis B vaccination in dialysis patients with end-stage renal disease.

Searching
MEDLINE and Current Contents were searched; the search terms were reported. Selected specialist journals were searched manually, as were reference lists in published trials and reviews. The search was limited to studies published between 1980 and 2005. There were no language restrictions. Abstracts and interim reports of trials were excluded.

Study selection
Study designs of evaluations included in the review
Prospective controlled trials were eligible for inclusion. One of the included studies was described as randomised and four as being placebo-controlled and double-blind. No further information about the design of the individual studies was reported.

Specific interventions included in the review
Studies comparing thymopentin plus hepatitis B vaccine with hepatitis B vaccine alone were eligible for inclusion. Plasma-derived and recombinant DNA hepatitis B vaccines were included, regardless of dose and route of administration. The vaccines used in the included studies were plasma-derived Heptavax-B and Hecvac-B and recombinant Engerix-B. The vaccine was given intramuscularly and thymopentin subcutaneously in all studies. Some studies used primary vaccination, whilst others used revaccination after failure to respond to intramuscular vaccination. The vaccine and thymopentin schedules varied between studies. The number of thymopentin 50-mg doses given ranged from 3 to 27 across the studies.

Participants included in the review
Studies in patients on maintenance haemodialysis or peritoneal dialysis were eligible for inclusion. Studies in patients with positive serology for the hepatitis B virus (HBV) antigen (HBsAg), antibodies to HBsAg (HBsAb) or the human immunodeficiency virus were excluded. Studies in renal transplant recipients and patients with predialysis renal insufficiency were also excluded. All of the participants in the included studies were chronic haemodialysis patients who had undergone bicarbonate dialysis thrice weekly for 3 or 4 hours per session. Some studies reported the time on dialysis: apparent mean values varied from 11 to 42 months. Men and women were included in those studies that reported the gender, and the mean age reported varied from 53 to 69 years.

Outcomes assessed in the review
The outcome of interest was the seroresponse rate to vaccination, defined as an HBsAb production level of 10 IU/mL. The outcome analysed in the review was failure to respond to vaccination. Side-effects were another outcome.

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, only that there was full agreement between reviewers on inclusion and exclusion according to the pre-specified criteria.
Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers extracted the data independently and reached consensus. Data were extracted to determine the serological response for patients who completed treatment. The results were presented as an odds ratio (OR) with 95% confidence interval (CI) for each study.

Methods of synthesis
How were the studies combined?
Meta-analysis was used to calculate the combined OR and 95% CI for failure to respond to vaccination for vaccine plus adjuvant thymopentin compared with vaccine alone. Pooled estimates of effect were calculated using the DerSimonian and Laird random-effects model. The authors reported adding 0.5 to each cell of the contingency table for studies that presented sparse data, which probably refers to studies with no events in one group. Data from patients who did not complete treatment were excluded from the analysis. Funnel plots were used to assess publication bias.

How were differences between studies investigated?
A chi-squared test of statistical heterogeneity was applied in the meta-analysis. Subgroup analyses, apparently not predefined, were undertaken to investigate sources of heterogeneity in the overall pooled analysis. The subgroup analyses reported were of studies of non-responder patients on maintenance haemodialysis, studies using recombinant vaccine, Italian studies, and studies using higher thymopentin doses (>50 mg x 9). A Galbraith plot was also shown.

Results of the review
Eleven studies including 272 patients were included. The data were obtained from six published reports, four of which reported two or three studies.

The pooled analysis of all studies showed no significant difference in failure to give a protective vaccine response between vaccine plus thymopentin and vaccine alone, (OR 0.677, 95% CI: 0.285, 1.605). The studies were statistically highly heterogeneous (p=0.0001). Asymmetry in the funnel plot was not statistically significant (p=0.17).

The subgroup analysis of five studies that used higher doses of thymopentin (50 mg x 9) showed a statistically significant difference in vaccine response in favour of adjuvant thymopentin (OR 0.181, 95% CI: 0.085, 0.398). Heterogeneity was not statistically significant (p=1.0). Asymmetry in the funnel plot was statistically significant (p=0.01). The other subgroup analyses showed no statistically significant difference between adjuvant thymopentin and control.

It was reported that no local or systemic side-effects occurred after thymopentin and/or HBV vaccine.

Cost information
The cost of thymopentin was quoted as 65 euros per 50 micrograms.

Authors’ conclusions
Thymopentin in higher doses significantly improved the seroresponse of dialysis patients to the hepatitis B vaccine. The limited number of patients precluded definitive conclusions.

CRD commentary
The review addressed a clear question and predefined the criteria for inclusion. A limited number of sources were searched for relevant studies. Procedures to minimise bias in the study selection process were not reported. Steps were
taken to minimise errors in the data extraction but study quality, and hence the potential for bias in the results of the included studies, was not assessed.

Details of the individual studies and the analysis were poorly reported, making it difficult to appraise the appropriateness of the data pooling and the reliability of the findings. The design of the included studies was particularly vague and the actual data from which the individual study results were derived were not shown. The reported subgroup analyses appear to have been decided on sight of the results and the findings need to be interpreted very cautiously. The authors’ conclusion is based on an observation that needs to be confirmed by more robust research.

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

**Practice:** The authors stated that the best strategy for HBV vaccination in end-stage renal disease requires evaluation of HBV endemicity and the cost of vaccine and adjuvants at the local level.

**Research:** The authors stated that large randomised trials with follow-up are needed to confirm the results from this review.

**Funding**
Project Glomerulonephritis.

**Bibliographic details**

**PubMedID**
16696803

**DOI**
10.1111/j.1365-2036.2006.02923.x

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adjuvants, Immunologic; Aged; Female; Hepatitis B /immunology /prevention & control; Hepatitis B Vaccines /immunology /therapeutic use; Humans; Kidney Failure, Chronic /immunology; Male; Middle Aged; Prospective Studies; Randomized Controlled Trials as Topic; Renal Dialysis; Thymopentin /administration & dosage

**AccessionNumber**
12006002457

**Date bibliographic record published**
31/05/2007

**Date abstract record published**
31/05/2007

**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.