The efficacy of thymosin in the treatment of chronic hepatitis B virus infection: a meta-analysis

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Authors' objectives
To conduct a meta-analysis to evaluate the efficacy of thymosin for the treatment of chronic hepatitis virus infection.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched for articles written in the English language. Additional studies were identified by examining the reference lists of trial publications and review articles, and by contacting the principal investigators of eligible trials.

Study selection
Study designs of evaluations included in the review
Only prospective randomised controlled trials (RCTs) with a minimum treatment duration of 24 weeks were included.

Specific interventions included in the review
Comparisons of thymosin with placebo or standard care were included. The included studies used thymosin at a dose of 900 microg/m2 or 1.6 mg (thrice weekly subcutaneous injection), as well as thymosin-alpha1 and thymosin fraction 5 at a dose of 90 microg/m2 (twice weekly subcutaneous injection).

Participants included in the review
Hepatitis B virus (HBV) infection. The trials had to include patients who were HBV DNA-positive by non-polymerase chain reaction assays, and who had elevated alanine transaminase levels.

Outcomes assessed in the review
Studies were included if they reported end-of-treatment and/or sustained virological and/or biochemical responses. Adverse event outcomes were also included.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the papers for inclusion in the review.

Assessment of study quality
The methodological quality of the trials was assessed on the basis of the following standards: clearly specified inclusion and exclusion criteria; concealment of randomisation; baseline equivalence of treatment groups; blindness; and completeness of follow-up. A point was given for each standard satisfied, according to the description contained within the text of each trial. A quality score was generated by summing the standards; this ranged from 0 (no standard satisfied) to 6 (all standards satisfied). The authors do not state how the papers were assessed for quality, or how many of the reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted the data from the included studies. The following data were extracted: the number of patients randomised to each group; the treatment regime; the duration of follow-up; and the treatment outcomes at the end of treatment and/or during the post-treatment follow-up period.

Methods of synthesis
How were the studies combined?
The odds ratios (ORs) of the main outcomes in the thymosin-treated group, over those in the control group, were used as the measure of efficacy. In addition, the 95% confidence interval (CI) for the combined OR was calculated. The results of the included studies were combined using the fixed-effect method of DerSimonian and Laird (see Other Publications of Related Interest no.1). When the heterogeneity test was significant (p=0.10 or lower), a random-effects model was also applied to see how much it changed the conclusion. The methods proposed by Egger et al. and Tang and Liu were used to detect publication bias (see Other Publications of Related Interest nos.2-3).

How were differences between studies investigated?
A chi-squared test was used to identify heterogeneity between the included trials.

**Results of the review**
Five (n=353) RCTs with seven valid comparisons were included in the meta-analysis.

**Virological response.**

End of treatment (5 comparisons, n=267): the combined OR was 0.56 (95% CI: 0.20, 1.52).

Significant heterogeneity was found between outcomes reported at 6 months (p=0.00277) and 12 months (p=0.055), so a random-effects model was also used to combine the data.

Six-month follow-up (5 comparisons, n=291): the ORs were 1.67 (95% CI: 0.83, 3.37) and 1.86 (95% CI: 0.58, 5.99) when using the fixed-effect and random-effects models, respectively, to combine the results.

Twelve-month follow-up (3 comparisons, n=207): the ORs were 2.67 (95% CI: 1.25, 5.68) and 2.70 (95% CI: 1.18, 6.19) when using the fixed-effect and random-effects models, respectively, to combine the results.

**Biochemical response.**

End of treatment (4 comparisons, n=257): the combined OR was 0.86 (95% CI: 0.44, 1.68).

Six-month follow-up (3 comparisons, n=209): the combined OR was 0.86 (95% CI: 0.45, 1.64).

Twelve-month follow-up (2 comparisons, n=108): the combined OR was 1.20 (95% CI: 0.51, 2.83).

**Adverse events.**

Local discomfort at the injection site was reported. Apart from this, there were no systemic or constitutional symptoms or biochemical abnormalities as a result of thymosin treatment.

**Authors’ conclusions**
Thymosin was effective in suppressing viral replication of chronic HBV infection, but the effect was delayed until 12 months after the cessation of treatment.

**CRD commentary**
This was a reasonably well-conducted review, although it contained some reporting errors. The inclusion criteria were appropriate to the review question. The search for relevant studies was relatively thorough, though some may have been missed by limiting the search to English language articles. The quality of the individual studies was assessed and appropriate details of the studies were tabulated. The studies were combined appropriately after using statistical methods to detect heterogeneity. However, although the studies did not differ in terms of statistical significance, the p-values for heterogeneity in the text differed from those presented in the forest plots. In the ‘biochemical response’ forest plot, the combined ORs at the end of treatment and at 6 months are both 0.86, but the 6-month combined OR is incorrectly plotted to indicate a (non significant) result favouring thymosin.
Implications of the review for practice and research

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

Research: The authors state 'future research is warranted to study the efficacy of combination therapy of thymosin with interferon or antiviral agents in the treatment of chronic HBV infection'.

Bibliographic details

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Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
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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.