Comparison of the efficacy of thymosin alpha-1 and interferon alpha in the treatment of chronic hepatitis B: a meta-analysis

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CRD summary
The authors concluded that six months of thymosin alpha-1 therapy was safe and effective in inhibiting hepatitis B virus replication in patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B virus. Overall, the authors' conclusions are likely to be reliable, but should be interpreted with some degree of caution given the absence of a formal validity assessment.

Authors' objectives
To compare the efficacy of thymosin alpha-1 (Tα1) versus interferon alpha (IFNα) in the treatment of patients with chronic hepatitis B virus.

Searching
MEDLINE and EMBASE were searched from 1966 to August 2007 for articles published in English. Search terms were reported. Reference lists of trial publications and review articles were searched and the authors of identified trials were contacted to identify any further studies.

Study selection
Prospective randomised controlled trials (RCT) comparing the use of thymosin alpha-1 and interferon alpha for a minimum of 24 weeks in the treatment of chronic hepatitis B virus were eligible for inclusion. Included studies were of thymosin alpha-1 in doses of 1.6mg twice weekly compared to 500MU interferon alpha three times weekly over a period of six months. Inclusion criteria for patients were HBV DNA-positive plus elevated alaninetransaminase levels. Included studies were of both hepatitis B e antigen-negative (HBeAg-negative) and hepatitis B e antigen positive (HBeAg-positive) patients with mean alaninetransaminase levels ranging from 141.6 IU/L to 191.5 IU/L. The mean age of patients ranged from 40 to 47 years and the majority were male.

Outcomes eligible for inclusion were virological response (defined as the disappearance of hepatitis B virus DNA plus the loss of HBeAg in HBeAg-positive patients or the loss of hepatitis B virus DNA in HBeAg-negative patients), biochemical response (defined as normalisation of alaninetransaminase levels) and complete response (both virological and biochemical response). In order to be eligible for inclusion, studies should report outcomes both at the end of treatment and more than 6 months post-treatment. Included studies reported both biological and virological outcomes at the end of treatment and at six months follow-up.

Studies of patients with different forms of viral hepatitis, or patients receiving anti-viral drugs other than thymosin alpha-1 compared to IFNα, were excluded.

Two reviewers independently performed the study selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The numbers of patients showing a response in the intervention and comparator groups were extracted for each outcome. Odds ratios (OR) with 95% confidence intervals (CI) were calculated.

Data were extracted independently by two reviewers and principal investigators were contacted for further data or clarification where necessary.
Methods of synthesis
Results were combined using a combined OR with 95% CI using the DerSimonian and Laird method using either a fixed effects or random effects model depending on the presence of statistical heterogeneity. The combined OR was weighted according to the standard error of the OR of each trial. Statistical heterogeneity was assessed using the Cochran $\chi^2$ statistic. Publication bias was assessed using funnel plots and tested for asymmetry using Egger's test.

Results of the review
Four RCTs were included for review (n=199). Validity was not formally assessed. However, the authors report that in all four studies the groups were comparable at baseline and all four had clearly defined inclusion and exclusion criteria. None of the four studies were double blind and none reported on allocation concealment.

At six months follow up, thymosin alpha-1 resulted in significantly greater suppressed viral replication (OR = 3.71, 95% CI: 2.05, 6.71, p<.0001) and normalised alaninetransaminase levels (OR=3.12, 95%CI: 1.74, 5.62, p=0.0001) compared to interferon alpha. Immediately following treatment there was no difference between the two groups in virological or biological response. Patients receiving interferon alpha were significantly more likely to show a complete response at the end of treatment compared to patients receiving thymosin alpha-1 (OR 0.54, 95%CI: 0.30, 0.97, p=0.04). However, patients receiving thymosin alpha-1 were significantly more likely to show a complete response at the end of the six month follow up period (OR=2.69, 95%CI: 1.47, 4.91, p=0.001) compared to patients receiving interferon alpha. There was no evidence of statistical heterogeneity for any of the outcomes. There was no evidence of publication bias.

Minor side effects were noted with treatment with interferon alpha (flu-like symptoms, fatigue, irritability, headache and leucocytopenia). However, no serious adverse events were noted. The only adverse event reported with thymosin alpha-1 was local discomfort at the injection site.

Authors' conclusions
Six months of thymosin alpha-1 therapy was safe and effective in inhibiting hepatitis B virus replication in patients with HBeAg-negative chronic hepatitis B. Thymosin alpha-1 was better tolerated than interferon alpha and may gradually result in more sustained ALT normalisation and hepatitis B virus DNA/HBeAg loss.

CRD commentary
The review addressed a clear question with well-defined inclusion criteria. However, the inclusion of studies with HBeAg(-) patients limits the ability to generalise the results to HBeAg(+) patients. Furthermore, the majority of patients were male, so it was unclear to what extent the result may be generalised to females. The search was limited to two databases and only English language articles, therefore language bias could not be ruled out and relevant data may have been missed. The authors do not appear to have searched for unpublished articles, but publication bias was tested for and ruled out. Appropriate steps were taken in the study selection and data extraction processes to minimise reviewer error and bias. A formal validity assessment did not appear to have been carried out, although the authors did comment on some aspects of study quality. The decision to combine the studies in a meta analysis was appropriate and statistical heterogeneity was assessed. Overall, the authors' conclusions are likely to be reliable, but should be interpreted with some degree of caution given the absence of a formal validity assessment.

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

Research: The authors stated that further research is needed into the efficacy of thymosin alpha-1 combined with interferon alpha or other anti-viral agents in the treatment of chronic hepatitis B.

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