Treatment with lamivudine versus lamivudine and thymosin alpha-1 for e antigen-positive chronic hepatitis B patients: a meta-analysis

Zhang YY, Chen EQ, Yang J, Duan YR, Tang H

CRD summary
The authors concluded that among HBeAg-positive patients, thymosin alpha-1 and lamivudine combination therapy may be more effective than lamivudine monotherapy with superior rates of biochemical and virological responses and HBeAg seroconversion. The conclusions reflect the evidence presented and are likely to be reliable, but should be interpreted with caution given the limited quality of included studies.

Authors' objectives
To compare the effect of lamivudine monotherapy with that of lamivudine and thymosin alpha-1 combination therapy for the treatment of hepatitis B e antigen (HBeAg)-positive hepatitis B patients.

Searching
PUBMED, EMBASE, CBM, CNKI, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews were searched. Search dates spanned 1966 to September 2008. Search terms were reported. Further searches were done manually. Studies reported in English and Chinese were eligible.

Study selection
Randomised controlled trials (RCTs) that evaluated lamivudine monotherapy and combination therapy with lamivudine and Tα1 in patients of 18 to 75 years of age with a diagnosis of HBeAg-positive chronic hepatitis B (CHB) were eligible for inclusion. Patients also needed to have hepatitis B virus (HBV) DNA positivity for at least six months and elevated alanine transaminase levels. Monotherapy with lamivudine (100mg orally, daily) must have been for at least 52 weeks. Combination therapy must have been with lamivudine (100mg orally, daily) for at least 52 weeks. Tα1 (1.6mg subcutaneously, twice a week) must have been for at least 24 weeks. Published data needed to include biochemical and virological response rates, seroconversion rates (HBeAg to HBeAb) and adverse effects. Studies of patients with antibodies to human immunodeficiency virus, hepatitis C, D or E virus and patients with decompensated liver disease, other forms of liver disease or a history of malignancy were excluded.

Study follow-up periods ranged from 0 to 12 months. Therapy periods varied: thymosin alpha 1 (six to 13 months) and lamivudine (12 to 18 months). The authors stated that most studies were conducted in China.

Two authors independently selected studies for inclusion. Disagreements were resolved by discussion among reviewers.

Assessment of study quality
Study quality was assessed (in accordance with the Cochrane format) based on adequacy of randomisation, allocation concealment, blinding and description of withdrawals and dropouts. Quality was classified as either A (low risk of bias), B (moderate risk of bias) or C (high risk of bias).

The authors did not state how many reviewers assessed study quality and how any disagreements were resolved.

Data extraction
Two authors independently extracted the numbers of patients in each group with outcomes of interest. Discrepancies were resolved by discussion. Authors of primary studies were contacted for additional information where necessary.

Methods of synthesis
Dichotomous data were presented as relative risk (RR). Continuous outcomes were presented as weighted mean difference (WMD). Studies were combined using fixed-effect or random-effects methods, depending on the absence or
presence of significant heterogeneity. Statistical heterogeneity between studies was assessed using the $X^2$ and $I^2$ tests.

**Results of the review**

Eight RCTs were included (n=583 patients). The follow-up periods ranged from 0 to 12 months. The quality of four studies was rated category B and four were category C. Groups were comparable at baseline in all studies. Four studies reported withdrawal rates. None of the studies were blinded and none clearly reported allocation concealment.

**Biochemical response:** Compared to lamivudine monotherapy, combination therapy with Tα1 and lamivudine was more effective at the end of treatment (RR 1.16, 95% CI 1.04 to 1.30; eight studies) and at the end of 12 months follow-up (RR 5.38, 95% CI 3.13 to 9.25; eight studies).

**Virological response:** Compared to lamivudine monotherapy, combination therapy with Tα1 and lamivudine was more effective at the end of treatment (RR 1.14, 95% CI 1.05 to 1.23; eight studies) and at the end of 12 months follow-up (RR 1.74, 95% CI 1.07 to 2.84; four studies).

**Seroconversion of HBeAg to HBeAb:** Compared to lamivudine monotherapy, combination therapy with Tα1 and lamivudine was more effective at the end of treatment (RR 2.98, 95% CI 2.22 to 4.01; eight studies) and at the end of 12 months (RR 5.91, 95% CI 3.15 to 11.10; four studies).

No significant heterogeneity was found for any of these analyses.

**Adverse events:** No serious adverse events were reported in either treatment group and studies reported no biochemical abnormalities.

**Authors’ conclusions**

Among HBeAg-positive patients, thymosin alpha-1 and lamivudine combination therapy may be more effective than lamivudine monotherapy with superior rates of biochemical and virological responses and HBeAg seroconversion.

**CRD commentary**

The review addressed a clear question and inclusion criteria (study designs, patients, interventions, outcomes) were appropriately defined. The restriction to studies in Chinese and English appeared reasonable given that the authors stated that most relevant studies were conducted in China. The search for unpublished studies was limited and so the possibility of publication bias could not be excluded. Study selection and data extraction were done in duplicate, which reduced risks of error and bias; it was unclear whether similar efforts were made in validity assessment. Study quality was assessed with appropriate criteria and results used to inform the synthesis. Statistical methods used to combine data appeared appropriate.

The conclusions reflect the evidence presented, but should be viewed with caution given the limited quality of included studies.

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

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

**Research:** The authors stated that additional high-quality, well-designed and adequately powered randomised controlled trials were needed to guide evolving standards of care for chronic hepatitis B.

**Funding**

National Basic Research Program of China (2007CB512902 and 2006CB504302) and Development Program of China (2008ZX10002-006).

**Bibliographic details**

MeSH
Antiviral Agents /therapeutic use; Drug Therapy, Combination; Hepatitis B e Antigens /blood; Hepatitis B, Chronic /drug therapy; Humans; Lamivudine /therapeutic use; Thymosin /analogs & derivatives /therapeutic use; Treatment Outcome

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.