Contemporary clinical research of traditional Chinese medicines for chronic hepatitis B in China: an analytical review

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CRD summary
This review concluded that some traditional Chinese medicines seemed as effective as conventional medicines for patients with chronic hepatitis B, and that further study of traditional Chinese medicines was warranted. The authors’ conclusions are appropriately cautious given the evidence available.

Authors’ objectives
This review had two objectives: firstly, to investigate the effectiveness of traditional Chinese medicines in the treatment of patients with chronic hepatitis B; secondly, to investigate which individual herbs were used most frequently in traditional Chinese medicine formulations, and which appeared to have the greatest efficacy in treating chronic hepatitis B.

Searching
Studies in Chinese or English were identified through a search of China National Knowledge Infrastructure database and PubMed from January 1998 to June 2008. Search terms were reported.

Study selection
Randomised controlled trials (RCTs), non-randomised controlled trials and summaries of clinical experience of patients with chronic hepatitis B, that compared traditional Chinese medicines with interferon or lamivudine, were eligible for inclusion. Chronic hepatitis B was defined as positivity for serum hepatitis B surface antigen and/or hepatitis B e antigen for more than six months, with elevated levels of serum alanine aminotransferase. Eligible studies were required to name the individual herbs in the traditional Chinese medicine formulations. Studies of single herbs were excluded.

Interferon therapy required a dose of at least 3 million units, administered three times a week for at least three months. Interferon-alpha, interferon-alpha1b, interferon-alpha 2b, or interferon-alpha 2a were eligible for inclusion. Lamivudine therapy required a dose of at least 100mg, administered once daily for at least 30 consecutive days.

Outcome measures included virological response (loss of serum hepatitis B e antigen and/or clearance of serum hepatitis B virus DNA) and normalisation of serum alanine aminotransferase levels at the end of treatment.

Comparisons included traditional Chinese medicine formulations only versus interferon or lamivudine; or traditional Chinese medicine formulations plus interferon or lamivudine versus interferon or lamivudine alone.

The authors did not state how the studies were selected for the review.

Assessment of study quality
Methodological quality was assessed using the Jadad scale, a 5-point scale evaluating randomisation, blinding and intention-to-treat. Studies were considered high quality if they scored 3 or more points.

The authors did not state how the validity assessment was performed.

Data extraction
The authors used the numbers of events in each group to extract odds ratios (OR) for dichotomous data and weighted mean differences (WMD) for continuous outcomes.

The number of times individual herbs were used in different traditional Chinese medicine formulations was recorded to determine the frequency with which particular herbs were used in traditional Chinese medicine formulations used to treat chronic hepatitis B.
The authors did not state how many reviewers performed the data extraction.

**Methods of synthesis**
The pooled odds ratios and corresponding 95% confidence intervals (CIs) were calculated using a random-effects model. Statistical heterogeneity was assessed using the $I^2$ test. Publication bias was assessed using funnel plots.

Subgroup analysis investigated higher quality studies.

**Results of the review**
Fifty-three RCTs were analysed to determine the effectiveness of traditional Chinese medicines on chronic hepatitis B. Two hundred and thirty studies were used to describe the traditional Chinese medicines used. Overall study quality was poor. Of the RCTs, none reported the methods used for randomisation, allocation concealment or blinding. Sixteen RCTs had a Jadad score of 3 points; 37 had a score of 2 points.

**Traditional Chinese medicine versus interferon** (16 RCTs; n=1,918 patients): Traditional Chinese medicine had a significantly better effect on normalising serum alanine aminotransferase levels compared with interferon treatment alone (OR 2.42, 95% CI 1.51 to 3.89), although significant heterogeneity was detected ($I^2=58.7\%$). Traditional Chinese medicine and interferon were equivalent in reducing serum hepatitis B e antigen (OR 1.60, 95% CI 1.00 to 2.54) and clearing serum hepatitis B virus deoxyribonucleic acid (OR 1.31, 95% CI 0.87 to 1.98).

**Traditional Chinese medicine plus interferon versus interferon alone** (18 RCTs; n=1,738 patients): Traditional Chinese medicine plus interferon significantly reduced serum hepatitis B e antigen (OR 2.17, 95% CI 1.74 to 2.72) compared with interferon treatment alone, as well as improving clearance of serum hepatitis B virus DNA (OR 2.05, 95% CI 1.59 to 2.65) and improving normalisation of serum alanine aminotransferase levels (OR 3.07, 95% CI 2.35 to 4.00). No significant heterogeneity was detected.

**Traditional Chinese medicine versus lamivudine** (six RCTs; n=723 patients): Traditional Chinese medicines were significantly more effective than lamivudine for normalising serum alanine aminotransferase levels (OR 1.96, 95% CI 1.15 to 3.22), although significant heterogeneity was detected ($I^2=60.8\%$). No differences between treatment groups were observed for the reduction in serum hepatitis B e antigen or the clearance of serum hepatitis B virus DNA.

**Traditional Chinese medicine plus lamivudine versus lamivudine alone** (14 RCTs; n=1,548 patients): Traditional Chinese medicine plus lamivudine significantly reduced serum hepatitis B e antigen (OR 2.54, 95% CI 1.95 to 3.32) compared with lamivudine alone, improved clearance of serum hepatitis B virus DNA (OR 3.20, 95% CI 2.09 to 4.92), and improved normalisation of serum alanine aminotransferase levels (OR 3.40, 95% CI 2.45 to 4.70). No significant heterogeneity was detected.

The review presented data of the most commonly used herbs in the traditional Chinese medicine formulations. Four herbs were reported in detail: *Astragalus* (Huang Qi), *Polygonum cuspidatum* (Hu Zhang), Radix et rhizoma rhei (Da Huang), and *Phyllanthus urinaris* (Ye Xian Zhu).

Subgroup analyses of 16 higher quality RCTs (Jaded score=3) did not influence the results.

Publication bias was not detected.

One of the authors disclosed financial links with several pharmaceutical companies.

**Authors' conclusions**
Some traditional Chinese medicines seemed effective as alternative remedies for patients with chronic hepatitis B. Further study of traditional Chinese medicines in the treatment of chronic hepatitis B is warranted, both in pre-clinical models of hepatitis B virus infection and in higher quality RCTs worldwide.

**CRD commentary**
This review addressed a clear question supported by appropriate inclusion criteria. Relevant databases were searched, although there did not appear to be any attempts to identify unpublished data. It was unclear whether steps to reduce reviewer bias and error were undertaken for study selection, data extraction or validity.

Results were pooled using meta-analysis and heterogeneity was assessed. The authors recognised some of the methodological difficulties with the review, specifically the poor quality of the included studies.

The authors’ conclusions appeared to reflect the evidence available and are appropriately cautious.

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

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

**Research:** The authors stated that further study of traditional Chinese medicines in the treatment of chronic hepatitis B is warranted, both in pre-clinical models of hepatitis B virus infection and in higher quality RCTs worldwide.

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