Chinese herbal medicine and interferon in the treatment of chronic hepatitis B: a meta-analysis of randomized, controlled trials

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Authors' objectives
To examine the effectiveness of Chinese herbal medicine, either alone or in combination with interferon (IFN)-alpha, in treating chronic hepatitis B.

Searching
The following databases were searched with no language restrictions: TCMLARS from 1984 to 2000; MEDLINE from 1966 to 2000; the Cochrane Database of Systematic Reviews from 1992 to 2000; CISCOM (no search dates given); EMBASE and Excerpta Medica from 1974 to 2000; and AMED from 1985 to 2000. The keywords and subject headings included 'hepatitis B', 'hepatitis B, chronic', 'drugs, Chinese herbal', 'medicine, Chinese traditional', 'medicine, oriental traditional', 'interferon' and 'interferons'. In addition, article bibliographies, nonindexed medical and professional journals, and the authors' libraries (Chinese language and English language) and files were searched manually. A senior investigator and collaborator at the China Academy of Sciences was contacted for additional published and unpublished data. Two of the review's authors translated the Chinese language articles.

Study selection

Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that reported the use of Chinese herbal medicine versus IFN-alpha, or Chinese herbal medicine combined with IFN-alpha versus IFN-alpha alone, for the treatment of hepatitis B were eligible for inclusion in the review. Chinese herbal medicine was defined as the 311 botanical and animal-product medicines that are commonly used in clinical practice by practitioners of traditional Chinese medicine, and which are listed in a current herbal medical textbook used at the Shanghai University of Traditional Chinese Medicine (see Other Publications of Related Interest no.1). A range of different Chinese herbal treatments were reported in the review. These included kurorinone, bufotoxin and actual plant species, e.g. Artemesia capillaris, Astragalus membranaceus, Peonia rubra, Polygonum multiflorum, Poria cocos and Pseudostellaria heterophylla; a full list was provided in the review.

The eligible forms of IFN-alpha for combined treatment or control included IFN-alpha, IFN-alpha-1b, IFN-alpha-2a and IFN-alpha-2b. To define a standardised control regimen, only studies in which the control group used IFN-alpha at a dose of at least 1 million units administered 3 times weekly were included. Studies in which the control group used very low doses of IFN-alpha, or different comparison treatments such as gamma-IFN, other drugs or other herbal treatments, were excluded.

Participants included in the review
Participants with chronic hepatitis B were eligible for inclusion in the review. People with chronic active hepatitis B and chronic persistent hepatitis B were included in the review. Chronic cases of hepatitis B infection were defined in most included studies as those in which positive hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) serum markers, and hepatitis B virus (HBV) DNA genetic markers, persisted for at least 6 months. The average age of the included participants ranged from 14.8 to 38.5 years.

Outcomes assessed in the review
The studies had to provide data on the numbers of responders and nonresponders for any of three dichotomous end points. The outcomes assessed in the review were HBsAg seroversion, HBeAg seroreversion and HBV DNA seroreversion, evaluated at the end of 3 months of treatment. Outcome data at long-term follow-up were eligible for inclusion in the review, but none were found.
How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
A modified scale, based on the method of Jadad et al. (see Other Publications of Related Interest no.2), was developed. This limited the assessment of study quality to how the studies randomised the patients and handled drop-outs or withdrawals. The maximum possible score was 3; a low score was 0 or 1, while a high score was 2 or 3. Two reviewers, who were blinded to the author, affiliation and journal title, reviewed the studies.

Data extraction
Two reviewers, who were blinded to the author, affiliation and journal title, reviewed the studies. The following data were extracted using standardised forms: publication year; diagnosis; average patient age; the definition of diagnosis used; the Chinese herbal medicine treatment used; the type of IFN-alpha used; the total number of participants in each treatment arm; and the number of treatment responders in each treatment arm for any of the end points (HBsAg, HBeAg and HBV DNA). Any disparities in the data extraction were resolved through a consensus process in which a third investigator served as the arbitrator.

The relative risk (RR) of cure was calculated, along with 95% confidence intervals (CIs), as the probability of seroconversion in the treated group divided by the probability of seroconversion in the control group. In four of the studies there were individual contingency table cells with no patients. In calculating the RR for these, the value 0.5 was added to all four cells of the contingency tables. Four studies with missing data were excluded from the analysis.

Methods of synthesis
How were the studies combined?
The studies were combined statistically in a meta-analysis within two groupings: Chinese herbal medicine alone versus IFN-alpha; and Chinese herbal medicine combined with IFN-alpha versus IFN-alpha alone. Further subgroup analyses were carried out where two or more studies reported the use of the same specific active compounds of Chinese herbal medicine. The summary RRs and 95% CIs across these groups were calculated as a weighted average, using a random-effects model (see Other Publications of Related Interest no.3). Publication bias was tested with a regression asymmetry test (see Other Publications of Related Interest no.4).

How were differences between studies investigated?
A variance-based method was used to assess the heterogeneity of treatment effects within subsets.

Results of the review
Twenty-seven RCTs (n=2,062) were included in the review. Two studies had a three-arm design that evaluated Chinese herbal medicine alone and Chinese herbal medicine combined with IFN-alpha, both versus IFN-alpha alone.

All the studies were of low quality, and each had a modified Jadad score of 0 or 1.

Chinese herbal medicine as sole treatment: patients using Chinese herbal medicine alone were significantly more likely to achieve seroreversion of HBsAg levels than were control patients using IFN-alpha (RR 2.00, 95% CI: 1.35, 2.97). Chinese herbal medicine alone was equivalent to IFN-alpha with respect to seroconversion of HBeAg (RR 1.20, 95% CI: 0.99, 1.49) and HBV DNA (RR 0.94, 95% CI: 0.80, 1.11).

Chinese herbal medicine combined with IFN-alpha: patients receiving combined therapy were significantly more likely than those receiving IFN-alpha alone to achieve seroconversion for all three outcomes. The RR was 2.08 for HBsAg (95% CI: 1.45, 2.96), 1.64 for HBeAg (95% CI: 1.39, 1.94) and 1.58 for HBV DNA (95% CI: 1.35, 1.85).

Chinese herbal medicine active component bufotoxin combined with IFN-alpha (2 studies): patients receiving a combination of bufotoxin and IFN-alpha were significantly more likely to achieve seroreversion of HBeAg (RR 1.50,
95% CI: 1.09, 2.08) and HBV DNA (RR 1.75, 95% CI: 1.24, 2.47) than those treated with IFN-alpha alone. There was no significant difference for HBsAg (RR 2.16, 95% CI: 0.99, 4.65).

Chinese herbal medicine active component kurorinone alone (2 studies): kurorinone appeared to be equivalent to IFN-alpha in its effect on seroconversion of HBeAg (RR 0.93, 95% CI: 0.68, 1.27) and HBV DNA (RR 0.88, 95% CI: 0.66, 1.16). Neither of the 2 studies reported seroreversion for HBsAg.

**Authors' conclusions**
Chinese herbal medicine may have potential therapeutic value in the treatment of chronic hepatitis B infection. However, because the studies reviewed were generally of a poor quality, no firm conclusions could be drawn.

**CRD commentary**
The review question and the study selection criteria were stated clearly. The literature search seems to have been very comprehensive, with no language restrictions applied and ample attempts to identify additional relevant material. The statistical tests conducted seem to have been appropriate for the analyses undertaken, and there was good, clear presentation and discussion of the findings. Some minor in-text errors are nevertheless present. For example, the conclusion that kurorinone used in combination therapy is promising for further investigation when, in fact, the studies of kurorinone were not combination therapies and showed no statistical benefit of this active component over the control. The findings of the tests for publication bias and heterogeneity were not reported.

The authors' conclusions seem appropriately cautious given the methodological limitations of the studies reviewed.

**Implications of the review for practice and research**
Practice: The authors state that Chinese herbal medicine may have potential therapeutic value in the treatment of chronic hepatitis B infection.

Research: The authors state that the Chinese herbal medicine active components bufotoxin and kurorinone, used in the combination therapies identified in the review, appear to be promising initial targets for further investigation. It is possible that further investigation in well-designed trials may help answer the question of whether Chinese herbal medicine can be effective for treating chronic hepatitis B. Given the significant public health hazard of chronic hepatitis B and the high rates of nonresponse to IFN therapy, continued and more carefully conducted research could be helpful in identifying more effective therapies. Future investigations should examine treatments of longer treatment.

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