Chinese Herbal Medicine and Interferon in the Treatment of Chronic Hepatitis B: A Meta-Analysis of Randomized, Controlled Trials

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Objectives. This meta-analysis was conducted to examine the effectiveness of Chinese herbal medicine (either alone or with interferon alfa) in treating chronic hepatitis B.

Methods. We searched the TCMLARS, AMED, CISCOM, EMBASE, MEDLINE, and Cochrane Collaboration databases and then hand-searched the articles' bibliographies.

Results. Chinese herbal medicine significantly increased seroreversion of HBsAg and was equivalent to interferon alfa in seroreversion of HBeAg and hepatitis B virus (HBV) DNA; Chinese herbal medicine combined with interferon alfa significantly increased seroreversion of HBsAg, HBeAg, and HBV DNA. The Chinese herbal medicine active component bufotoxin combined with interferon alfa significantly increased HBeAg and HBV DNA seroreversion. The Chinese herbal medicine active component kurorinone was equivalent to interferon alfa in seroreversion of HBeAg and HBV DNA.

Conclusions. Although the quality of existing studies was poor, these data suggest that further trials of Chinese Herbal Medicine and interferon in chronic hepatitis B infection are justified. (*Am J Public Health.* 2002;92:1619–1627)

Traditional Chinese medicine is an established segment of the health care delivery system in China. In planning for allocation of health care resources, an important question for China's health care authorities is whether traditional Chinese medicine functions best as a stand-alone therapy or in close integration with allopathic medical care. However, little formal assessment of its clinical effectiveness has been conducted. In this study, we sought to evaluate the clinical evidence for its effectiveness in the treatment of chronic hepatitis B and to examine the quality of the published data.

As one of the core techniques used within traditional Chinese medicine, Chinese herbal medicine is commonly used in China in the treatment of hepatitis. In this meta-analysis of randomized, controlled trials we examined the effectiveness of Chinese herbal medicine in the treatment of chronic hepatitis B when used as a stand-alone therapy and when used in combination with interferon alfa. The control group in each case was patients treated with interferon alfa alone.

Infection with hepatitis B virus is a significant public health concern. Worldwide, an estimated 2 billion people are infected with the hepatitis B virus (HBV).[1] A total of 350 million people have the chronic form of hepatitis B infection, 75% of whom live in Asia.[1] Chronic infection increases the risk for primary liver cancer.[1] Endemic hepatitis B infection in Asia's large population contributes to primary liver cancer's position as the fourth leading cause of cancer death worldwide (after lung, stomach, and colorectal cancers).[2–4]

Successful treatment of hepatitis B infection has long been defined as loss of detection of hepatitis B surface antigen (HBsAg). Meta-analysis has shown that HBsAg clearance occurs in only 6% of patients with chronic hepatitis B who are treated with interferon alfa.[5] Observational studies have shown that such clearance occurs spontaneously in 4% to 29% of people with chronic infection.[6–8] However, patients can develop HBsAg-negative chronic infection, a clinical course with a more serious prognosis than that of patients who are HBsAg positive.[1] Therefore, some authors support the use of hepatitis B e antigen (HBeAg) and HBV DNA as markers of active viral replication and infectivity.[9–12] HBeAg clearance occurs in 18% to 40% of patients with chronic hepatitis B who are treated with interferon alfa and spontaneously in 15% to 60% of people with chronic infection.[13] Furthermore, patients can also develop HBeAg-negative chronic infection, which, as with HBsAg-negative patients, signals a poor prognosis.[1,13]

Herbal medicine is in common use in many parts of the world. A 1997 survey estimated that 34% of the American public use alternative medicine; among the survey respondents, 12% reported the use of herbal medicine within the prior 12 months.[14] In China, Chinese herbal medicine is used as a treatment adjunct or alternative to interferon alfa and accounts for 30% to 50% of total medicine consumption,[3] with low cost and low toxicity. Interferon alfa, by contrast has a very high cost and significant toxicities.[15–18]

English-language journals have published few randomized trials of Chinese herbal medicine for the treatment of hepatitis.[19–23] A far larger body of literature exists in Chinese-language journals. For centuries, textbooks have discussed treatment strategies handed down in the oral and literary tradition of Chinese herbal therapy. Over the past 50 years, modern Chinese-language medical journals have more formally assessed the effectiveness of these treatment strategies. From case reports came observational studies and, over the past decade, randomized, controlled trials. Although these medical journals report only studies from the past 50 years, these data represent a distillation of the accumulated historical experience of the body of traditional Chinese medicine. The field has grown substantially, from 1 published randomized, controlled trial of Chinese herbal medicine for the treatment of chronic hepatitis B in 1991 to 221 in 1999. Until recently, however, time-consuming searching by hand was the only means of accessing Chinese-language data sources.

Online availability of the Chinese-language TCMLARS database (Traditional Chinese Medicine Language Acquisition and Retrieval System; available at http://www.cintcm.ac.cn) now allows rapid searching of journal abstracts to quickly locate clinical trials data published in China after 1984. TCMLARS contains more than 330 000 references and abstracts to literature on traditional Chinese medicine, drawn from more than 600 Chinese biomedical journals and 100 specialty journals. Searching is straightforward, and scanned articles can be ordered via e-mail. Approximately 10% of the abstract database has been translated into English.

Using TCMLARS and searches of Western medical literature, we examined 2 hypotheses: (1) that treatment with Chinese herbal medicine could serve as an alternative therapy when interferon alfa is not available or acceptable, and (2) that Chinese herbal medicine used in combination with interferon alfa could enhance the effectiveness of interferon alfa. We were interested in assessing the effectiveness of Chinese herbal medicine when used either as a stand-alone therapy or in combination with interferon alfa and also in examining the quality of the published data.

METHODS

Study Selection

We searched for articles in TCMLARS (1984–2000), MEDLINE (1966–2000), the Cochrane Database of Systematic Reviews (Cochrane Collaboration, 1992–2000), CISCOM (Centralised Information Service for Complementary Medicine), EMBASE (Excerpta Medica, 1974–2000), and AMED (Allied & Complementary Medicine Resources, 1985–2000), with articles in all languages included for consideration. We used the following keywords and medical subject headings: hepatitis B; hepatitis B, chronic; drugs, Chinese herbal; medicine, Chinese traditional; medicine, oriental traditional; interferon; and interferons. These resources were supplemented by the handsearching of articles' bibliographies, nonindexed medical and professional journals, and the Chinese-language and English-language libraries and files of the authors. Two authors (M.M. and M.B.) translated the Chinese-language articles. We searched for additional data, both published and unpublished, through communications with a senior investigator and collaborator at the China Academy of Sciences (J.G.). To define a standardized control regimen, we included only studies in which the control group used interferon alfa at a dosage of at least 1 million units administered 3 times weekly; we excluded studies in which the control group used very low doses of interferon alfa, different comparison treatments such as gamma interferon, other drugs, or other herbal treatments.

In the first stage of our systematic review, we identified studies describing the use of Chinese herbal medicine and interferon alfa in the title or abstract (n = 587). We retained for further review studies in which interferon alfa was administered to the control group (n = 49). For the meta-analysis, we retained only those 27 studies (1) that were randomized, controlled trials of Chinese herbal medicine alone (vs interferon alfa) or Chinese herbal medicine combined with interferon alfa (vs interferon alfa) for the treatment of hepatitis B (Table 1) and (2) that provided data on the number of responders and nonresponders for any of the 3 endpoints: HBsAg (n = 18 studies), HBeAg (n = 27), and HBV DNA (n = 20). We defined Chinese herbal medicine as the 311 botanical and animal-product medicines that are commonly used in clinical practice by practitioners of traditional Chinese medicine and enumerated in a current herbal medical textbook used at the Shanghai University of Traditional Chinese Medicine.[50] When we found multiple reports of the same patient data, we selected for review only the most recently published data (n = 1).

We retained studies that reported the use of different forms of interferon alfa (interferon alfa, n = 20 studies; interferon alfa-1b, n = 2; interferon alfa-2a, n = 3; interferon alfa-2b, n = 2) in the treatment or control groups. Previous research has documented similarities in the effectiveness of the different forms of interferon alfa in the treatment of hepatitis B.[51–53]

Data Abstraction

Two reviewers (M.M. and M.B.), who were blinded to author, affiliation, and journal title, reviewed the 27 studies. The following data were abstracted through standardized forms: publication year; diagnosis; average patient age; definition of diagnosis used; Chinese herbal medicine treatment used; type of interferon alfa used; interferon alfa doses; whether the treatment arm involved Chinese herbal medicine alone or Chinese herbal medicine combined with interferon alfa; the total number of subjects in each treatment arm; and the number of treatment responders in each treatment arm for any of the endpoints HBsAg, HBeAg, and HBV DNA. Any disparities in data abstraction were resolved through a consensus process in which a third investigator served as arbitrator (J.M.C.).

Quality Scoring

Five of these trials compared an injected active ingredient extracted from a Chinese herbal medicine with injected interferon alfa[19,24,38,43,45] and thus could have included double-blinding within the study design. However, in the remaining 22 studies, blinding was obviously not possible because those studies compared an orally administered Chinese herbal medicine with injected interferon alfa. Thus, we created a modified scale based on the method of Jadad,[54,55] limiting our assessment of study quality to how studies randomized patients and handled dropouts or withdrawals (low score = 0 or 1; high score = 2 or 3; maximum possible total score = 3).

Statistical Analysis

We used the Stata statistical software package (version 6.0; Stata Corp, College Station, Tex) for data management and analysis. We calculated relative risk of cure from the data in the original studies for use in the meta-analysis. These relative risks were calculated as the probability of seroreversion in the treated group divided by the probability of seroreversion in the control group. Thus, relative risk values greater than 1.0 are consistent with a beneficial effect of Chinese herbal medicine used alone (vs interferon alfa) or Chinese herbal medicine in combination with interferon alfa (vs interferon alfa). In 4 of the studies, we encountered individual contingency table cells with no patients.[26,33,37,48] In calculating relative risk for these studies, the

TABLE 1—Chinese Herbal Medicine (CHM) for Chronic Hepatitis B: Study Diagnoses and Herbal Medicines Used

Author	Quality Score[a]	Diagnosis	CHM or CHM + IFN-α Group, Average Age ± Range	IFN-α Group, Average Age ± Range	Herbal Treatment
Cai[24] (1997)	0	CAH, CPH, CAH + LC	31.5 ± 10.3	35.4 ± 9.9	Kurorinone
Chen[19] (2000)	1	CHB	NS	NS	Kurorinone
Dai[25] (1998)	1	CAH, CPH	NS	NS	*Artemesia capillaris, Astragalus membranaceus, Peonia rubra*, *Polygonum multiflorum*, *Poria cocos*, *Pseudostellaria heterophylla*
Fu[26] (1997)	0	CHB	NS	NS	*Agrimonia*, *Astragalus membranaceus*, *Atractylodes alba*, *Carthamus tinctorum*, *Ligusticum wallichium*, *Codonopsis pilosula*, *Gardenia jasminoidis*, *Gentiana scabra*, *Glycyrrhiza uralensis*, *Imperata cylindrica*, *Peonia alba*, *Peonia rubra*, *Prunus persica*, *Poria cocos*, *Pueraria lobata*, *Rheum officinale*, *Salvia multiorrhiza*, *Sparganium longifolium*, *Schisandra chinensis*, *Curcuma longazedoaria*, *Zingiberis officinalis*, *Zizyphus jujuba*
Hao[27] (1996)	1	CHB, CPH	NS	NS	Ganpi jiaonang combination (ingredients not specified)
Huang[28] (1999)	1	CHB	32.5 ± 6.7	30.8 ± 5.6	*Phyllanthus*, pseudoginseng
Huang[29] (2000)	1	CHB	35.7 ± 11.3	37.2 ± 11.7	*Artemesia capillaris*, *Atractylodes alba*, bupleurum, *Glycyrrhiza uralensis*, *Hypericum japonicum*, *Magnolia officinalis*, *Polygonum cuspidatum*, *Polyporus umbellatus*, *Poria cocos*, *Rheum officinale*, *Salvia multiorrhiza*
Jing[30] (2000)	1	CHB	28.7 (NS)	27.6 (NS)	*Cuscuta chinensis*, *Ganoderma lucidum*, *Juglans regia*, *Sophora subprostata*
Li[31] (1998)	1	CHB	30.8 ± 5.7	32.8 ± 6.9	*Phyllanthus*, pseudoginseng
Li[32] (1999)	0	CHB	NS	NS	*Phyllanthus*, *Polygonum cuspidatum*, *Schisandra chinensis*
Li[33] (1997)	1	CAH	NS	NS	*Agrimonia pilosa*, *Isatis indigotica*, *Scutellaria barbata*, *Scutellaria baicalensis*, *Nidus vespae*, *Oldenlandia diffusa*, *Polygonum cuspidatum*, *Smilax glabra*
Li[34] (2000)	1	CHB	33.7 ± 7.8	31.0 ± 7.8	*Alpinia*, *Atractylodes alba*, bupleurum, *Coix lachryma-jobii*, *Curcuma longa*, *Dryopteris crassirhizo*, *Eclipta prostrate*, *Oldenlandia diffusa*, *Isatis indigotica*, *Loranthus parasiticus*, *Magnolia officinalis*, *Patrinia villosa*, *Pinellia ternata*, baijiangcao, *Scutellaria baicalensis*
Liu[35] (1999)	1	CHB	CHM group: 32.6 ± 14.6; CHM + IFN-α group: 34.6 ± 17.8	35.7 ± 20.5	*Agrimonia pilosae*, *Bruca javanica*, litchi, *Dryopteris crassirhizo*, *Punica granatum*, *Prunus mume*, *Siegesbeckia orientalis*, *Stemonia japonica*
Lu[36] (1992)	1	CAH, CPH	NS	NS	*Achyranthis bidentata*, aloe, *Amyda sinensis*, *Artemesia capillaris*, *Astragalus membranaceus*, *Atractylodes alba*, *Citrus medica*, *Curcuma longa*, *Eclipta prostrate*, *Gallus gallus domesticus*, *Gardenia jasminoidis*, *Gentiana macrophylla*, *Imperata cylindrica*, *Isatis indigotica*, *Lithospermum arnebia*, *Loranthus parasiticus*, mouton, *Oldenlandia diffusa*, *Peonia rubra*, *Polygonum cuspidatum*, *Salvia multiorrhiza*
Qian[37] (1999)	1	CAH	37.4 (NS)	36.4 (NS)	*Carthamus tinctorum*, *Ligusticum wallichium*, *Lithospermum arnebia*, *Polygonum cuspidatum*, pseudoginseng, *Salvia multiorrhiza*, *Scutellaria baicalensis*
Shen[38] (2000)	1	CHB	31.2 (NS)	32.3 (NS)	Bufotoxin
Song[39] (1994)	0	CHB	15.6 (NS)	14.8 (NS)	*Aconite carmichaeli*, *Agastache rugosa*, *Amomum cardamom*, *Astragalus membranaceus*, *Atractylodes alba*, *Citrus reticulata*, *Epimedium*, *Glycyrrhiza uralensis*, *Panax ginseng*, *Poria cocos*, *Rehmannia glutinosa*
Wang[40] (1997)	1	CAH, CPH	NS	NS	*Astragalus membranaceus*, *Cassia tora*, chouteng, dibo, guicao, huangpi, longye, *Salvia multiorrhiza*
Wang[41] (2000)	1	CHB	38.5 (NS)	36.4 (NS)	*Eupolyphaga*, hirudo, qichan, tabanus
Wang[42] (2000)	1	CHB	33.4 (NS)	35.0 (NS)	*Astragalus membranaceus*
Wu[43] (1997)	1	CHB	38.2 ± 6.5	36.4 ± 7.9	*Salvia multiorrhiza*
Wu[44] (1998)	1	CHB	36.5 (NS)	36.0 (NS)	*Atractylodes alba*, *Amyda sinensis*, bupleurum, amomum, *Citrus reticulata*, *Dioscorea opposita*, *Glycyrrhiza uralensis*, *Lycium chinensis*, *Panax ginseng*, *Pinellia ternata*, *Peonia alba*, *Poria cocos*, *Rheum officinale*, *Scutellaria barbata*, *Trionyx sinensis*
Zhang[45] (1999)	1	CHB	28.4 (NS)	27.6 (NS)	Bufotoxin
Zhang[46] (1997)	1	CHB	36 (NS)	34.5 (NS)	Long dan xie gan tang (ingredients not specified)
Zhang[47] (1999)	1	CHB	20–50 (NS) for both CHM & CHM+ IFN-α groups	20–50 (NS)	*Bupleurum*, erhoutao, *Hypericum japonicum*, *Imperata cylindrica*, *Panax ginseng*, jixueteng, tianwangye, wuahuaxueteng
Zhao[48] (1996)	1	CAH; CPH	36.0 ± 11.1	34.2 ± 13.4	*Astragalus membranaceus*, *Prunus persica*, *Curcuma longa zedoaria*
Zhou[49] (1999)	1	CHB	36.2 ± 10.3	35.6 ± 11.0	*Atractylodes alba*, *Astragalus membranaceus*, *Crinis carbonisatus*, *Prunus persica*, *Phyllanthus*, *Polygonum multiflorum*, *Poria cocos*, *Rehmannia glutinosa*, *Salvia multiorrhiza*, *Schisandra chinensis*, *Taraxacum mongolicum*

Note. CAH = chronic active hepatitis B; CHB = chronic hepatitis B; CPH = chronic persistent hepatitis B; IFN-α = interferon alfa; LC = liver cancer; NS = not specified.
[a]Points awarded for modified Jadad scale criteria (how studies randomized patients and handled dropouts or withdrawals): low score = 0 or 1; high score = 2 or 3; maximum possible total score = 3.

value 0.5 was added to all 4 cells of the contingency table.[56] Confidence intervals for the relative risks were estimated by the Woolf method.[57] Studies with missing data were excluded from analysis (n = 4). We used the Egger et al. regression asymmetry test[58] to examine our meta-analysis data for publication bias

We constructed our groupings for meta-analysis as follows: (1) to assess the effectiveness of Chinese herbal medicine as a stand-alone therapy, all studies of Chinese herbal medicine alone (vs interferon alfa) were analyzed together (Figure 1; Table 2); (2) to assess the effectiveness of Chinese herbal medicine as an adjunct to interferon alfa, all studies of Chinese herbal medicine combined with interferon alfa (vs interferon alfa) were analyzed together (Figure 1; Table 3); (3) to examine the effectiveness of specific active components extracted from Chinese herbal medicines, subanalyses of those active components were conducted when 2 or more studies reporting use of the same active component were available. Within each of these groupings, the outcome we studied was seroreversion of 3 dichotomous endpoints: HBsAg, HBeAg, and HBV DNA. Using these endpoints, we calculated the treatment effect of Chinese herbal medicine alone (vs interferon alfa) and Chinese herbal medicine combined with interferon alfa (vs interferon alfa); we report these results as relative risk of cure, with 95% confidence intervals. A relative risk of cure > 1 indicates effectiveness of the treatment evaluated.

We calculated the summary effect estimates across the above-mentioned groups of studies as a weighted average, using the random-effects model of DerSimonian and Laird.[59] We used a variance-based method to assess the heterogeneity of treatment effect within subsets.[60]

RESULTS

In our initial screening, we identified 587 abstracts in which the title, the abstract, or both mentioned the use of both Chinese herbal medicine and interferon: 583 by electronic searches of the TCMLARS database, 2 by electronic searches of MEDLINE, 1 by hand-searching the bibliographies of each of the identified journals, and 1 by electronic searches of EMBASE (this reference was also identified by MEDLINE).

Of these 587 studies, 27 met our inclusion criteria (see "Methods" section). All 27 were randomized, controlled trials of patients with chronic hepatitis B, treated with Chinese herbal medicine treatment alone (vs interferon alfa; n = 15) or Chinese herbal medicine combined with interferon alfa (vs interferon alfa; n = 14), with interferon alfa administered at dosages of at least 1 million units 3 times weekly. Two studies had a 3-arm design, thus contributing data to both the treatment group using only Chinese herbal medicine and the treatment group using Chinese herbal medicine combined with interferon alfa.[35,47] We identified 2 individual studies with data on the active component kurorinone[19,24] and 2 individual studies with data on bufotoxin.[38,45]

All studies with the exception of the Lu et al.[36] study used 1 of the 2 diagnostic standards for chronic hepatitis B currently recognized in China: the 1990 Shanghai and 1995 Beijing diagnostic protocols, which define chronic cases of hepatitis B infection as those in which positive HBsAg and HBeAg serum markers and HBV DNA genetic marker persist for 6 months or more.[61] The Lu study used an older diagnostic standard, the 1984 Hainan protocol, which also defines chronic cases as those persisting for 6 months or more. All studies evaluated patients for treatment outcomes at the end of 3 months of treatment. Although we had hoped to find and report data on long-term follow-up, only 1 study provided such data.[21] Furthermore, all studies were of low quality, and each study had a modified Jadad scale 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 receiving interferon alfa (Figure 1; Table 2) (relative risk [RR] = 2.00; 95% confidence interval [CI] = 1.35, 2.97). Our evaluation suggested that Chinese herbal medicine used alone was equivalent to interferon alfa with respect to seroreversion 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 Interferon Alfa

Patients receiving combined therapy were significantly more likely than those receiving interferon alfa alone to achieve seroreversion (Figure 1; Table 3). This was true for all 3 outcomes: HBsAg (RR = 2.08; 95% CI = 1.45, 2.96), HBeAg (RR = 1.64; 95% CI = 1.39, 1.94), and HBV DNA (RR = 1.58; 95% CI = 1.35, 1.85).

Chinese Herbal Medicine Active Component Bufotoxin Combined With Interferon Alfa

Patients receiving a combination of bufotoxin and interferon alfa were significantly more likely than interferon alfa–treated control patients 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), but not of HBsAg (RR = 2.16; 95% CI = 0.99, 4.65).

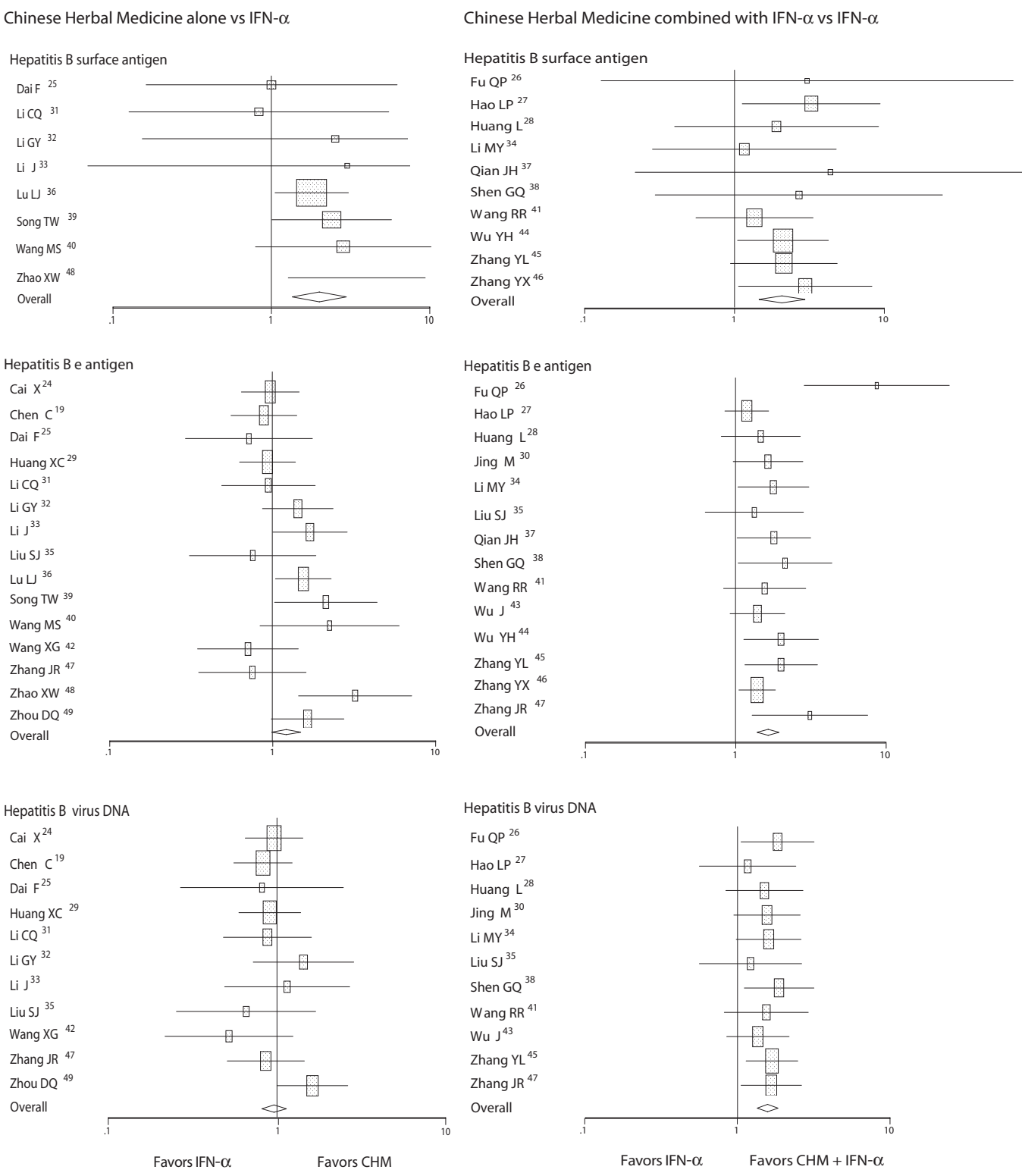
Chinese Herbal Medicine Active Component Kurorinone Alone

The Chinese herbal medicine active component kurorinone, when used alone, appeared to be equivalent to interferon alfa in its effect on seroreversion 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 employing kurorinone[19,24] reported seroreversion data on HBsAg, so we were not able to include that endpoint in this subanalysis.

DISCUSSION

Our meta-analysis data suggest that Chinese herbal medicine in the treatment of chronic hepatitis B infection may have potential therapeutic value; however, because the studies we found were of generally poor quality, we are unable to make firm conclusions.

Substantial limitations apply to these findings. Published studies from China were found to be more highly condensed than typical articles published in the Western literature, with key details of study design omitted, especially details concerning blinding of subjects and clinicians. We chose the Jadad scale to assess study quality because its straightforward and simple design makes it suitable for such studies.



Note. CHM = Chinese herbal medicine; IFN-α = interferon alfa. The diamond on each of the 6 plots represents the weighted average summary of the individual trials.

FIGURE 1—Meta-analysis forest plots for seroreversion among patients with chronic hepatitis B infection treated with Chinese herbal medicine: pooled relative risks and 95% confidence intervals, by trial.

TABLE 2—Seroreversion in Chronic Hepatitis B: Chinese Herbal Medicine (CHM) Alone vs Interferon Alfa (IFN-α)

Study	Seroconversion, No. of Responders/Total No. of Patients in Group: IFN-α	CHM	RR (95% CI)
Hepatitis B surface antigen[a]			
Dai[25] (1998)	2/15	2/15	1.00 (0.16, 6.20)
Li[31] (1998)	2/25	2/30	0.83 (0.13, 5.50)
Li[32] (1999)	1/32	3/38	2.53 (0.28, 23.1)
Li[33] (1997)	0/40	1/40	3.00 (0.13, 71.5)
Lu[36] (1992)	15/79	33/97	1.79 (1.05, 3.05)
Song[39] (1994)	5/30	20/50	2.40 (1.01, 5.72)
Wang[40] (1997)	2/11	33/64	2.84 (0.79, 10.1)
Zhao[48] (1996)	0/30	10/30	21.0 (1.29, 342)
Overall	27/262	104/364	2.00 (1.35, 2.97)
Hepatitis B e antigen[b]			
Cai[24] (1997)	23/50	28/63	0.97 (0.64, 1.45)
Chen[19] (2000)	17/29	15/29	0.88 (0.55, 1.41)
Dai[25] (1998)	7/15	5/15	0.71 (0.29, 1.75)
Huang[29] (2000)	28/60	26/60	0.93 (0.62, 1.38)
Li[31] (1998)	9/20	11/26	0.94 (0.49, 1.82)
Li[32] (1999)	13/32	22/38	1.43 (0.87, 2.35)
Li[33] (1997)	13/40	22/40	1.69 (1.00, 2.87)
Liu[35] (1999)	8/31	7/36	0.75 (0.31, 1.84)
Lu[36] (1992)	17/38	40/58	1.54 (1.04, 2.28)
Song[39] (1994)	6/21	23/38	2.12 (1.03, 4.37)
Wang[40] (1997)	3/11	39/64	2.23 (0.83, 5.98)
Wang[42] (2000)	12/31	9/33	0.70 (0.35, 1.44)
Zhang[47] (1999)	12/45	9/45	0.75 (0.35, 1.60)
Zhao[48] (1996)	5/20	12/15	3.20 (1.44, 7.12)
Zhou[49] (1999)	11/30	36/60	1.64 (0.98, 2.74)
Overall	184/473	304/620	1.20 (0.99, 1.49)
Hepatitis B DNA[c]			
Cai[24] (1997)	25/52	29/64	0.94 (0.64, 1.39)
Chen[19] (2000)	23/34	17/31	0.81 (0.55, 1.20)
Dai[25] (1998)	5/15	4/15	0.80 (0.27, 2.41)
Huang[29] (2000)	27/60	24/60	0.89 (0.59, 1.35)
Li[31] (1998)	10/18	11/23	0.86 (0.48, 1.56)
Li[32] (1999)	9/32	15/38	1.40 (0.71, 2.77)
Li[33] (1997)	8/40	9/40	1.13 (0.48, 2.62)
Liu[35] (1999)	8/31	6/36	0.65 (0.25, 1.66)
Wang[42] (2000)	12/31	6/33	0.51 (0.22, 1.22)
Zhang[47] (1999)	19/45	16/45	0.84 (0.50, 1.42)
Zhou[49] (1999)	12/30	38/60	1.58 (0.98, 2.56)
Overall	158/388	175/445	0.94 (0.80, 1.11)

Note. CI = confidence interval; RR = relative risk.
[a]Chi-square test for heterogeneity = 4.83 ($P = .68$); overall z score = 3.46 ($P = .001$).
[b]Chi-square test for heterogeneity = 25.56 ($P = .029$); overall z score = 1.82 ($P = .07$).
[c]Chi-square test for heterogeneity = 9.51 ($P = .049$); overall z score = –0.69 ($P = .049$).

In 22 of the 27 studies assessed in this meta-analysis, because the treatment group received orally administered Chinese herbal medicine and the control group received injected interferon alfa, blinding of subjects and clinicians was not possible. In such a study design, blinding could be achieved only if the treatment and control groups each received both oral and injected trial medications (i.e., the treatment group could receive true orally administered herbal medicine and placebo injection, and the control group could receive placebo orally administered herbal medicine and true interferon alfa injection).

Only 1 of our 27 studies[39] described the method of randomization used (unfortunately, this consisted of alternating case record numbers, which is not a truly random method). None of the other studies provided any details of the randomization method used, an unfortunate oversight given the availability of low-cost computers and free random number–generating software. Even more problematic was the lack of discussion in any study about whether the investigators knew which patients were randomized to receive treatment. However, failure to fully describe randomization procedures is not limited to Chinese medical journals. One study showed that as recently as 1994, 70% to 80% of trials published in Western journals did not adequately describe randomization.[62]

In future trials, we propose that Chinese investigators employ relatively simple measures such as random number–generating software for use in randomization and placebo trial drugs for use in comparing different therapies or in evaluating new and emerging extracted active components of Chinese herbal medicines. More thorough reporting of patient characteristics would also be helpful.

In these studies, subjects in both herbal medicine and interferon groups were treated for only 3 months. Because prior work has documented that long-term treatment with interferon alfa can almost double response rates,[63–65] future investigations with Chinese herbal medicine or Chinese herbal medicine combined with interferon alfa should examine longer treatment durations.

Our findings suggest that Chinese herbal medicines administered in combination with interferon alfa may augment the efficacy of

TABLE 3—Seroreversion in Chronic Hepatitis B: Chinese Herbal Medicine (CHM) Combined With Interferon Alfa (IFN-α), vs IFN-α

Study	Seroconversion, No. of Responders/Total No. of Patients in Group: IFN-α	CHM + IFN-α	RR (95% CI)
Hepatitis B surface antigen[a]			
Fu[26] (1997)	0/40	1/40	3.00 (0.13, 71.5)
Hao[27] (1996)	3/16	18/30	3.20 (1.11, 9.25)
Huang[28] (1999)	2/30	5/40	1.88 (0.39, 9.01)
Li[34] (2000)	3/30	4/35	1.14 (0.28, 4.71)
Qian[37] (1999)	0/36	2/42	4.30 (0.21, 86.8)
Shen[38] (2000)	1/30	3/34	2.65 (0.29, 24.1)
Wang[41] (2000)	6/25	8/25	1.33 (0.54, 3.29)
Wu[44] (1998)	7/30	29/60	2.07 (1.03, 4.17)
Zhang[45] (1999)	7/40	11/30	2.10 (0.92, 4.76)
Zhang[46] (1997)	4/34	12/35	2.91 (1.04, 8.15)
Overall	33/311	93/371	2.08 (1.45, 2.96)
Hepatitis B e antigen[b]			
Fu[26] (1997)	3/40	26/40	8.67 (2.85, 26.4)
Hao[27] (1996)	11/15	26/30	1.18 (0.84, 1.65)
Huang[28] (1999)	9/25	19/36	1.47 (0.80, 2.69)
Jing[30] (2000)	11/30	24/40	1.64 (0.96, 2.79)
Li[34] (2000)	11/32	22/36	1.78 (1.03, 3.07)
Liu[35] (1999)	8/31	12/35	1.33 (0.63, 2.82)
Qian[37] (1999)	11/36	23/42	1.79 (1.02, 3.15)
Shen[38] (2000)	7/28	17/32	2.13 (1.03, 4.36)
Wang[41] (2000)	9/25	14/25	1.56 (0.83, 2.91)
Wu[43] (1997)	19/43	24/39	1.39 (0.92, 2.11)
Wu[44] (1998)	9/28	36/56	2.00 (1.13, 3.55)
Zhang[45] (1999)	25/40	26/30	2.00 (1.15, 3.49)
Zhang[46] (1997)	5/34	16/35	1.39 (1.05, 1.83)
Zhang[47] (1999)	12/45	24/45	3.11 (1.28, 7.54)
Overall	150/452	309/521	1.64 (1.39, 1.94)
Hepatitis B DNA[c]			
Fu[26] (1997)	2/30	14/32	1.83 (1.06, 3.18)
Hao[27] (1996)	6/15	14/30	1.17 (0.56, 2.42)
Huang[28] (1999)	9/23	20/34	1.50 (0.84, 2.69)
Jing[30] (2000)	12/30	25/40	1.56 (0.95, 2.58)
Li[34] (2000)	13/33	24/38	1.60 (0.98, 2.61)
Liu[35] (1999)	8/31	11/35	1.22 (0.56, 2.64)
Shen[38] (2000)	10/25	21/28	1.88 (1.11, 3.17)
Wang[41] (2000)	8/20	13/21	1.55 (0.82, 2.91)
Wu[43] (1997)	17/43	21/39	1.36 (0.85, 2.18)
Zhang[45] (1999)	16/40	20/30	1.68 (1.14, 2.49)
Zhang[47] (1999)	19/45	32/45	1.67 (1.06, 2.63)
Overall	120/335	215/372	1.58 (1.35, 1.85)

Note. CI = confidence interval; RR = relative risk.
[a]Chi-square test for heterogeneity = 3.01 ($P = .96$); overall z score = 4.03 ($P = .00002$).
[b]Chi-square test for heterogeneity = 17.95 ($P = .16$); overall z score = 5.76 ($P = .00001$).
[c]Chi-square test for heterogeneity = 2.37 ($P = .99$); overall z score = 5.66 ($P = .00001$).

interferon. However, a better understanding of drug synergism between herbal medicines and interferon alfa is needed. A small number of studies have shown drug synergism between Chinese herbal medicines and interferons, suggesting, for example, that herbal medicines may boost endogenous interferon production.[66–68] These initial studies and their positive findings of synergism are important and can help inform future clinical investigations of combined-modality therapy for chronic hepatitis B.

In a previous review by the Cochrane Collaboration,[69] a search of the Chinese medical literature was limited to Western databases (which index few Chinese journals) and handsearching of 5 Chinese journals. Because that review did not use the TCMLARS database, it did not identify many of the primary trials found in this study. Our use of the TCMLARS database allowed us to more completely search all medical journals published in China, yielding 27 studies that focused specifically on comparing herbal therapy with a known reference standard, interferon alfa. In our review, TCMLARS was more effective than Western databases as a search tool for locating clinical studies on Chinese medicine, yielding 583 potentially useful studies, compared with 2 obtained from MEDLINE. TCMLARS may become an important new asset in literature review and meta-analysis of Chinese herbal medicine.

The Chinese herbal medicine active components bufotoxin[38,45] and kurorinone[19,24] used in the combination therapies identified in this 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 interferon therapy, continued and more carefully conducted research could be helpful in identifying more effective therapies. ■

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M. McCulloch was involved in conception and design of the study; acquisition, analysis, and interpretation of data; drafting and critical revisions of the manuscript; and statistical expertise. M. Broffman was involved in conception and design, analysis and interpretation of data, critical revisions, and supervision. J. Gao was involved in acquisition, analysis, and interpretation of data; critical revisions; and technical support. J.M. Colford Jr was involved in conception and design, analysis and interpretation of data, drafting and critical revisions of the manuscript, statistical expertise, technical support, and supervision.

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