Criteria Grid
Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C

Best Practice/Intervention:	Cheng D. et al. (2014) Peginterferon plus Chinese herbal therapy is associated with a higher virological response than only peginterferon therapy in chronic hepatitis C. European Journal of Clinical Microbiology & Infectious Diseases, 33(3):433-438.
Date of Review:	February 8, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **Chronic HCV patients treated with peginterferon or peginterferon and chinese herbal therapy** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **Shaanxi, China** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	meta-analysis; review of randomized control trials to compare the efficacy of peginterferon therapy versus peginterferon plus Chinese herbal therapy for the treatment of chronic hepatitis C
The best practice/intervention has utilized an evidence-based approach to assess:				
Efficacy	☒	☐	☐	Use of random-effects model for the variability among trials. When patients discontinue therapy, data analyzed using intention-to-treat principle

Effectiveness	☒	☐	☐	
The best practice/intervention has been evaluated in more than one patient setting to assess:				
Efficacy	☒	☐	☐	A total of 858 patients, 421 underwent therapy with peginterferon plus Chinese herbs and 437 underwent therapy with peginterferon
Effectiveness	☒	☐	☐	

	YES	NO	N/A	COMMENTS
The best practice/intervention has been operationalized at a multi-country level:	☒	☐	☐	Used published studies from worldwide biomedical databases (The Cochrane Central Register of Controlled Trials, Medline, Science Citation Index, EMBASE, China National Knowledge Infrastructure, Wanfang Database, and China Biomedical Database)
There is evidence of capacity building to engage individuals to accept treatment/diagnosis	☐	☒	☐	
There is evidence of outreach models and case studies to improve access and availability	☐	☒	☐	
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	As long as same journal database and similar eligibility criteria are implemented
Evidence of manpower requirements is indicated in the best practice/intervention	☐	☒	☐	
Juried journal reports of this treatment, intervention, or diagnostic test have occurred	☒	☐	☐	*European Journal of Clinical Microbiology & Infectious Diseases*
International guideline or protocol has been established	☐	☒	☐	

The best practice/intervention is easily accessed/available electronically	☐	☒	☐	Available to download with a price from http://link.springer.com/
Is there evidence of a cost effective analysis? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
How is the best practice/intervention funded? ***Please got to Comments section***	☐	☐	☐	This study was partly supported by the Fundamental Research Funds for the Central Universities, the China Postdoctoral Science Foundation, the National Natural Science Foundation of China, the National Science and Technology Support Program, and a Public Service Platform Grant and Science Foundation of Shaanxi Province
Other relevant information: _____	☐	☐	☐	- First meta-analysis to compare standard peginterferon therapy with peginterferon plus Chinese herbal therapy - Evidence suggests combined therapty of peginterferon plus Chinese herbal therapy more efficacious Limitations: - Low quality of included RCTs from full accounting of all randomized patients, follow-up, and blinded methods - Publication bias

Eur J Clin Microbiol Infect Dis (2014) 33:433–438
DOI 10.1007/s10096-013-1973-y

ARTICLE

Peginterferon plus Chinese herbal therapy is associated with a higher virological response than only peginterferon therapy in chronic hepatitis C

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Received: 23 July 2013 / Accepted: 28 August 2013 / Published online: 11 September 2013

Abstract Traditional Chinese herbal therapies are widely used for the treatment of chronic hepatitis C (CHC) in China and several Asian countries. The aim of this study was to perform a meta-analysis of randomized controlled trials (RCTs) comparing peginterferon therapy with peginterferon plus Chinese herbal therapy for the treatment of CHC. The Cochrane Central Register of Controlled Trials, Medline, Science Citation Index, EMBASE, China National Knowledge Infrastructure, Wanfang Database, and China Biomedical Database were searched to identify RCTs that evaluated the virological response of CHC patients to peginterferon therapy and peginterferon plus Chinese herbal therapy. We statistically combined data using a fixed-effects meta-analysis according to the intention-to-treat principle. The literature search yielded 905 studies and nine RCTs composed of 858 patients matched the selection criteria. Overall, sustained virological response (SVR) was significantly higher in patients treated with peginterferon plus Chinese herbs than in patients treated with peginterferon alone (81 % vs. 64 %, respectively; odds ratio, 2.60; 95 % confidence interval: 1.32–5.14; $p < 0.05$). A combined therapy of peginterferon plus Chinese herbs was also superior to peginterferon therapy in achieving an early viral response (EVR, 80 % vs. 70 %, respectively), a viral response at week 24 of treatment (82 % vs. 73 %, respectively), and end-of-treatment viral response (ETVR, 73 % vs. 62 %, respectively). The combined therapy resulted in fewer relapses, fewer adverse events, and more rapid alanine transaminase normalization; however, both treatments yielded a similar rapid viral response (RVR, 53 % vs. 57 %, respectively). The current evidence suggests that combined therapy of peginterferon plus Chinese herbs yields a higher viral response and results in fewer relapses and fewer adverse events than peginterferon therapy alone.

Introduction

Approximately 300 million people in the world, including about 40 million people in China, are believed to be infected with the hepatitis C virus (HCV). HCV has become the most important cause of chronic hepatitis and end-stage liver disease worldwide [1–5]. Peginterferon plus ribavirin has been used as the standard treatment for chronic hepatitis C (CHC) patients, with relatively high sustained virological responses (SVRs) [6–9]. However, this therapy results in frequent side effects and a large number of patients are not suitable candidates for the long-term administration of peginterferon for a variety of reasons [10, 11]. Complementary and alternative medicine (CAM) has, therefore, been introduced to increase the virological response and to improve the adverse effects [12]. The widespread use of CAM is emphasized among people with chronic diseases [13]. As one of the main components of CAM, Chinese medicine has been used as a front line medicine and has been widely utilized in medical

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systems, especially in China and some parts of Asia [9, 12]. Adverse reactions to Chinese herbs are rare and negligible when compared to those commonly produced by pharmaceutical drugs. In recent years, a combined therapy of Chinese herbs plus interferon was found to be associated with higher SVRs than interferon alone in CHC [12]. Whether the combination of Chinese herbs and peginterferon therapy could achieve higher virological responses than peginterferon therapy alone remains unclear. The aim of this study was to assess these randomized clinical trials (RCTs) for the efficacy of peginterferon therapy compared with peginterferon plus Chinese herbal therapy.

Materials and methods

Search strategy

The meta-analysis protocol used in this study was designed by Dr. Enqi Liu and Dr. Sihai Zhao. A search of the literature was conducted for studies that reported the therapeutic effects of peginterferon with or without Chinese herbal medicine therapy in CHC patients. The Cochrane Central Register of Controlled Trials, PubMed, Science Citation Index, EMBASE, China National Knowledge Infrastructure, Wanfang Database, and China Biomedical Database were searched to identify RCTs published in the field of antiviral therapy for CHC. The keywords used in the literature searches included the following: chronic hepatitis C, hepatitis C virus, HCV, Chinese herbal therapy, Chinese traditional medicine, Chinese traditional drugs, herbs, peginterferon, pegylated interferon, treatment, and trial.

Eligibility criteria

The inclusion criteria included the following: (i) studies that were designed to compare the therapeutic effects of peginterferon therapy with peginterferon plus Chinese herbal therapy in CHC patients [patients co-infected with hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV) were excluded); (ii) patients treated for at least 24 weeks; and (iii) publications written in any language. Reports of duplicated studies were excluded by examining the author list, parent institution, sample size, and results.

Study selection and data collection

Two authors (Daxin Cheng and Yafeng Li) independently screened titles and abstracts for potential eligibility and the full texts for final eligibility. We extracted the data from the included trials independently for quantitative analyses, and any disagreement was subsequently resolved by discussion. The quantitative data included the sample size, the pre-treatment patient characteristics, including age range and gender, the type of peginterferon, the doses of Chinese herbs, peginterferon, and ribavirin, SVR, rapid virological response (RVR), early viral response (EVR), end-of-treatment viral response (ETVR), alanine transaminase (ALT) normalization, and adverse effects.

Outcome measure

The primary outcome was the SVR, and other measures included the RVR, EVR, ETVR, relapse rate, ALT normalization, and occurrence of adverse events.

Assessment of study quality

Two authors (Yafeng Li and Ruihan Liu) independently assessed the quality of the included studies according to the descriptions provided by the authors of the included trials. The methodological quality of the trials was assessed based on adequate sequence generation, allocation concealment, blinding, management of incomplete outcome data, and early stoppage for beneficial reasons.

Synthesis of the results

In this meta-analysis, we used a random-effects model because of the anticipated variability among trials with regard to patient populations. The measure of association used in this meta-analysis was the odds ratio (OR) with a 95 % confidence interval (CI). The summary OR with 95 % CI was calculated by the RevMan 5.1 software using the fixed-effects model (Review Manager Version 5.0 for Windows; The Cochrane Collaboration, Oxford, UK). A statistically significant result was assumed when the 95 % CI did not include one. Heterogeneity was explored using a Chi-squared test, and the quantity of heterogeneity was measured using the I^2 statistic. When patients were discontinued, the data were analyzed according to the intention-to-treat principle. Patients who did not achieve the selected endpoints were considered to have failed therapy; the total number of patients was used as the denominator.

Results

Literature search

Figure 1 shows the results of the study screen. The literature search yielded 905 studies, nine of which matched the selection criteria [14–22]. All studies compared peginterferon plus Chinese herbal therapy with peginterferon therapy. There was unanimous agreement between the two authors (Daxin Cheng and Yafeng Li) regarding the selection of relevant articles.

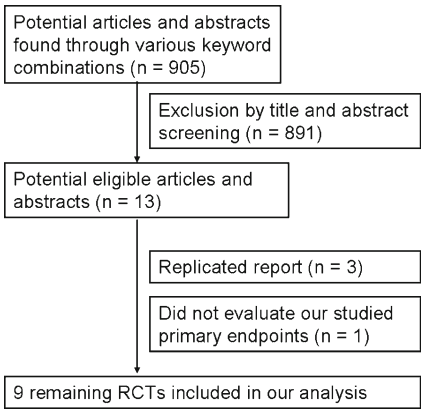

Fig. 1 Flow diagram of the reviewed randomized controlled trials (RCTs)

Clinical trial characteristics

All RCTs included were published as full-length articles. The patients included in the nine trials were randomly assigned to accept peginterferon plus Chinese herbal therapy or peginterferon therapy. Of the 858 patients, 421 underwent therapy with peginterferon plus Chinese herbs and 437 underwent therapy with peginterferon. Excluding Nie et al.'s study, all studies were single-center trials. The baseline characteristics of the nine included trials are summarized in Tables 1 and 2. Information on the methodological quality was incomplete in the majority of eligible RCTs; only Nie et al.'s study reported sequence generation and incomplete outcome data. The methodological quality of all eligible RCTs was not high.

Comparison of peginterferon plus Chinese herbal therapy and peginterferon therapy

In this study, the combined therapies of peginterferon and Chinese herbs were superior to peginterferon therapy alone. Patients treated with peginterferon plus Chinese herbs achieved a higher EVR, ETVR, and SVR than patients treated with only peginterferon, but the two therapies yielded similar RVRs. There was no significant difference in achieving an RVR for patients treated with peginterferon plus Chinese herbs compared to the patients treated with peginterferon alone (53 % vs. 57 %, respectively; OR: 0.85; 95 % CI: 0.59–1.24). The combined EVR was higher for patients treated with peginterferon plus Chinese herbs compared to the patients treated with peginterferon alone (80 % vs. 70 %, respectively; OR: 1.72; 95 % CI: 1.19–2.48; $p<0.05$). The peginterferon plus Chinese herbs therapy was also superior to peginterferon therapy in achieving a viral response at 24 weeks and an ETVR (24th week: 82 % vs. 73 %, respectively; OR: 1.52; 95 % CI: 0.98–2.35; $p=0.06$; ETVR: 73 % vs. 62 %, respectively; OR: 1.82; 95 % CI: 1.14–2.90; $p<0.05$). The follow-up data showed that patients treated with peginterferon plus Chinese herbs also achieved a higher SVR than patients treated with peginterferon (81 % vs. 64 %, respectively; OR: 2.60; 95 % CI: 1.32–5.14; $p<0.05$) (Fig. 2). Patients treated with combined therapies also achieved significantly higher ALT normalization at both end-of-

Table 1 Characteristics of the trials included in the meta-analysis

References	Treatment	Sample size	Sex (male/female)	Genotype		Mean age	Duration (weeks)	Follow-up (weeks)
				1	Non-1			
Fu et al. [14]	PegINF+RBV+CH	32	24/8	–	–	32.7±14.5	48	0
	PegINF+RBV	30	21/9	–	–	29.2±16.2		
Ji et al. [15]	PegINF+RBV+CH	26	18/8	–	–	36.7±17.5	12	0
	PegINF+RBV	30	18/12	–	–	37.2±18.7		
Jing et al. [16]	PegINF+RBV+CH	26	21/5	–	–	40.1(17–56)	48	0
	PegINF+RBV	22	18/4	–	–	39.8(18–54)		
Nie et al. [17]	PegINF+RBV+CH	178	188/164	352	0	41.5±14.1	24[a]	0
	PegINF+RBV+placebo	174						
Qiu et al. [18]	PegINF+RBV+CH	40	42/58	100	0	49.2±10.6	48	24
	PegINF+RBV	60						
Sun [19]	PegINF+RBV+CH	30	17/13	9	21	44.7±17.4	24	0
	PegINF+RBV	30	15/15	10	20	37.9±14.8		
Wang et al. [20]	PegINF+RBV+CH	17	9/8	12	5	39±28	48	24
	PegINF+RBV	19	11/8	14	5	37±21		
Xie et al. [21]	PegINF+RBV+CH	42	23/19	–	–	41.6±10.3	48	24
	PegINF+RBV	42	21/21	–	–	39.9±17.6		
Zhang [22]	PegINF+RBV+CH	30	10/20	–	–	20–65	48	0
	PegINF+RBV	30	12/18	–	–	18–64		

[a] The designed duration of this trial was one year, with a one-year follow-up; the remaining data were held before analysis and publishing

PegIFN peginterferon, *RBV* ribavirin

Table 2 Interventions of the trials included in the meta-analysis

References	Intervention	
	Control	Treatment
Fu et al. [14]	Peginterferon α-2a (180 μg/week), RBV (1,000 mg/day)	Peginterferon α-2a (180 μg/week), RBV (1,000 mg/day), Chinese medicinal formula (taken twice daily for 24 weeks)
Ji et al. [15]	Peginterferon α-2a (180 μg/week), RBV (1,000 mg/day)	Peginterferon α-2a (180 μg/week), RBV (1,000 mg/day), Bingganning granules (Huangqi 15 g, Chaobaishu 15 g, Huzhang 15 g, Zhizi 15 g, Huhuanglian 6 g, Kushen 15 g; taken twice daily)
Jing et al. [16]	Peginterferon α-2a (180 μg/week), RBV (900–1,200 mg/day)	Peginterferon α-2a (180 μg/week), RBV (900–1,200 mg/day), Chinese medicinal formula (Chaihu 10 g, Yujin 10 g, Huangqi 30 g, Baihuasheshecao 30 g, Huzhang 15 g, Kushen 15 g, Chishaoyao 15 g, Danshen 20 g, Danggui 15 g, Fuling 15 g, Baishu 15 g; taken twice daily)
Nie et al. [17]	Peginterferon α-2a (180 μg/week), RBV (900 mg/day), and placebo	Peginterferon α-2a (180 μg/week), RBV (900 mg/day), Fuzhengjiedu prescription (basic herbs: Huangqi 15 g, Baishu 15 g, Huzhang 15 g, Kushen 15 g, Zhizi 15 g, Huhuanglian 6 g; taken twice daily)
Qiu et al. [18]	Peginterferon α-2a (180 μg/week), RBV (1,000 mg/day)	Peginterferon α-2a (180 μg/week), RBV (1,000 mg/day), Chinese medicinal formula (basic herbs: Baimaogen 20 g, Fuling 10 g, Yinchen 10 g, Zhihuangqi 10 g, Gancao 4 g; taken twice daily)
Sun [19]	Peginterferon α-2a (180 μg/week), RBV (900 mg/day)	Peginterferon α-2a (180 μg/week), RBV (900 mg/day), Chinese medicinal formula (Huangqi 15 g, Chaobaishu 15 g, Huzhang 15 g, Zhizi 15 g, Huhuanglian 6 g, Kushen 15 g, Dangshen 10 g, Chaihu 15 g; taken twice daily)
Wang et al. [20]	Peginterferon α-2a (180 μg/week), RBV (15 mg/kg/day for genotype 1 and 800 mg/day for genotype non-1)	Peginterferon α-2a (180 μg/week), RBV (15 mg/kg/day for genotype 1 and 800 mg/day for genotype non-1), Chinese medicinal formula (Huangqi 15 g, Baishu 10 g, Zhizi 15 g, Dangshen 10 g, Huzhang 8 g, Huhuanglian 6 g; taken once daily)
Xie et al. [21]	Peginterferon α-2a (180 μg/week), RBV (15 mg/kg/day)	Peginterferon α-2a (180 μg/week), RBV (15 mg/kg/day), Chinese medicinal formula (Huangqi, Dangshen, Kushen, Diyu, Huangjing, Danggui, Chuanqiong, Shudi, Baishao, Gancao; taken once daily)
Zhang [22]	Peginterferon α-2a (180 μg/week), RBV (900 mg/day)	Peginterferon α-2a (180 μg/week), RBV (900 mg/day), Chinese medicinal formula (taken twice daily)

RBV ribavirin

treatment and follow-up [18], but the difference was not significant at the 24th week of treatment [17].

Safety profile evaluation

Treatment discontinuation due to severe adverse effects was not reported in any of the included trials. Many other adverse events were reported in the included trials (including thrombocytopenia, neutropenia, anemia, depression, fatigue, headache, insomnia, fever, nausea, and dyspnea). The overall adverse events or concurrent illnesses were less frequent in patients treated with peginterferon plus Chinese herbs than in patients treated with peginterferon alone according to the reports of the included trials [14, 16, 18, 20, 21].

Publication bias

The number of included trials was not enough to perform a funnel plot analysis to explore publication bias. In this meta-analysis, the mix of small and large trials seemed reasonable and yielded fairly consistent results. However, publication bias could not be completely avoided because only one of the included trials matched the high methodological quality criteria [17].

Discussion

CHC is an unsolved medical problem and has become a serious worldwide public health problem in both developed

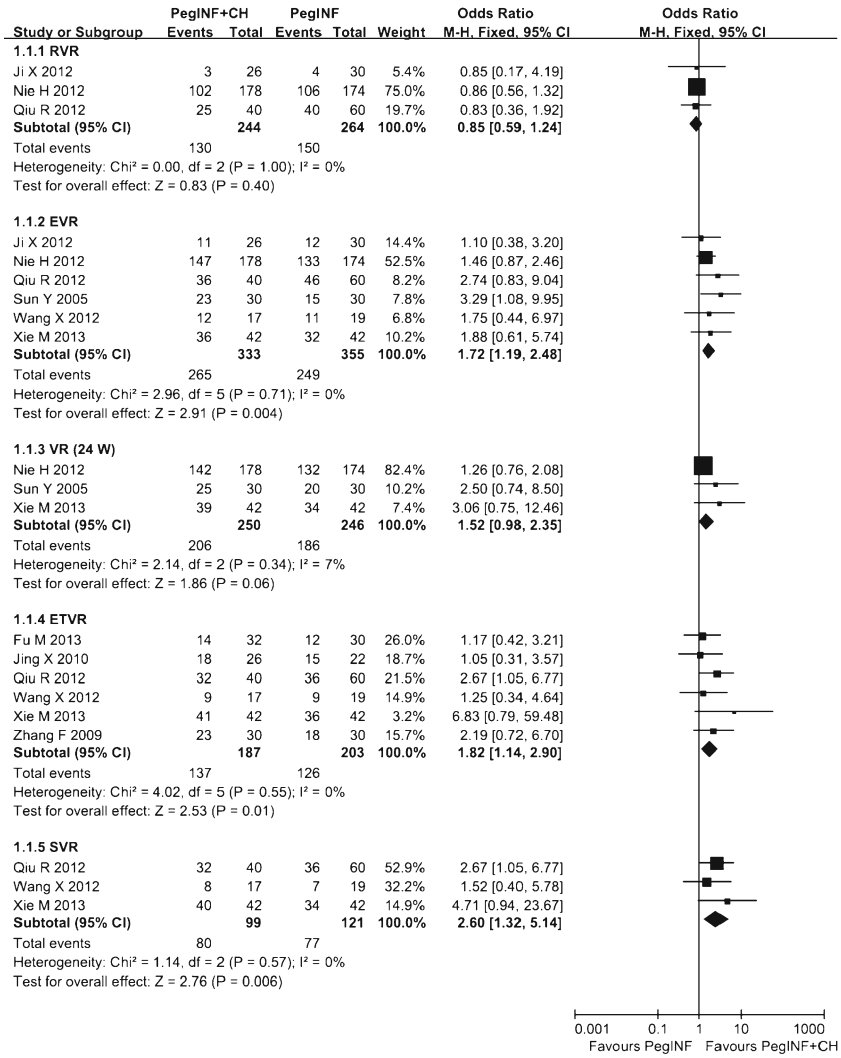

Fig. 2 Comparison of peginterferon plus Chinese herbal therapy versus peginterferon therapy alone in viral responses. *PegINF*, peginterferon; *CH*, Chinese herbs; *RVR*, rapid viral response; *EVR*, early viral response; *ETVR*, end-of-treatment viral response; *SVR*, sustained virological response; *CI*, confidence interval; test for heterogeneity: Chi-squared test with its degrees of freedom (d.f.) and *p*-value; inconsistency among results: I^2 test for overall effect; Z-statistic with *p*-value

and developing countries. Peginterferon plus ribavirin combination therapy is recommended for patients with CHC by the U.S. Food and Drug Administration (FDA) and the European Commission [23, 24]. Though peginterferon plus ribavirin combined therapy has been recommended, the achievement of an SVR, the expense, the frequency of adverse effects, and the large numbers of intolerant patients are not satisfactory. With rare adverse reactions, good tolerance, and less expense, Chinese herbs are commonly used as the first-line therapy for many chronic liver diseases, including HCV and HBV infections in Asia [12, 25]. Interferon plus Chinese herbs is associated with a higher SVR than interferon alone in CHC [12]. However, whether peginterferon plus Chinese herbs is associated with a higher SVR than peginterferon alone in CHC remains unclear.

In this study, we have summarized the available evidence from RCTs comparing peginterferon therapy with peginterferon plus Chinese herbal therapy for the treatment of CHC. Our results suggest that combination therapies of peginterferon and Chinese herbs could achieve significantly higher EVRs, ETVRs, and SVRs than peginterferon therapy alone. Though an RVR is another valuable predictor of an SVR, peginterferon plus Chinese herbal therapy achieved similar levels of RVR as peginterferon therapy [26, 27]. This finding could be related to the characteristics of Chinese herbs. Chinese herbs are compound drugs that usually cure the disease by long-term regulation of the immune system to improve its physical self-repairing capability. In this study, the SVR in peginterferon plus Chinese herbs combination therapy was about 81 %, which is higher than the peginterferon treatment results from both Chinese and Caucasian CHC patients [7, 28]. Combination therapies of interferon plus Chinese herbs have also shown superior ALT normalizations, safety profiles, and lower adverse effects. Chinese herbs have also been revealed to have anti-fibrotic and anti-inflammatory activity [14]. These findings suggested that Chinese herbs are associated with a higher virological response in the treatment of CHC patients when combined with peginterferon.

To the best of our knowledge, this study was the first meta-analysis to compare the standard peginterferon therapy with

peginterferon plus Chinese herbal therapy. Current evidence suggests that combined therapies of peginterferon plus Chinese herbal therapy appear to be more efficacious than peginterferon therapy alone and do not result in any additional safety problems. It is important to mention that there were limitations to the present meta-analysis. The quality of the included RCTs in this study was relatively low because the full accounting of all randomized patients, follow-up, and blinded methods were not used. Although the main worldwide biomedical databases were searched to identify potential RCTs, publication bias could not be avoided completely. In this study for SVR, there is no apparent heterogeneity, and the direction of the treatment effect is the same across all included trials.

Acknowledgments This work was partly supported by the Fundamental Research Funds for the Central Universities, the China Postdoctoral Science Foundation (201104669), the National Natural Science Foundation of China (81070250 and 81270348), the National Science and Technology Support Program (2012BAI39B02), and a Public Service Platform Grant and Science Foundation of Shaanxi Province (2010FWPT-15, 2012FWPT-03, 2012KJXX-07).

Conflict of interest The authors declare that they have no conflict of interest.

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