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Original Article

Peginterferon and Chinese herbs exert a combinatorial effect in HBeAg-positive chronic hepatitis B

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Abstract

Introduction: Traditional Chinese herbs are widely used for the treatment of chronic hepatitis B (CHB) in China. The aim of this study was to perform a meta-analysis of randomized controlled trials (RCTs) comparing peginterferon therapies with peginterferon plus Chinese herbal therapies in hepatitis B e antigen (HBeAg)-positive CHB patients.

Methodology: The main biomedical databases were searched to identify RCTs that compared the efficiency of peginterferon with peginterferon plus Chinese herbs in CHB patients.

Results: The literature search yielded 616 studies, and 8 RCTs (624 patients) matched the selection criteria. Combined therapies of peginterferon plus Chinese herbal therapies were superior to peginterferon therapies alone in achieving the serum HBV DNA clearance rate (64.5% vs. 45.0%), serum HBeAg clearance rate (47.4% vs. 33.5%), and HBeAg seroconversion rates (39.2% vs. 23.1%) at the end of treatment. Combined therapies were more effective than peginterferon alone therapies in the improvement of liver fibrosis related biomarkers, including hyaluronic acid, procollagen type III, type IV collagen, and lamina. Combined therapies also resulted in fewer relapses, fewer adverse events, and more rapid alanine transaminase normalization.

Conclusions: The current evidence suggests that peginterferon plus Chinese herbal therapies were associated with higher virological response than peginterferon alone in HBeAg-positive CHB patients.

Key words: peginterferon; Chinese herbs; chronic hepatitis B

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Introduction

Hepatitis B virus (HBV) infection is a serious global public health problem. Worldwide, an estimated two billion people have been infected with HBV. More than 240 million have chronic (long-term) liver infections, and 600,000 people die every year due to the acute or chronic consequences of hepatitis B [1]. A nationwide survey in China showed that the prevalence of hepatitis B surface antigen (HBsAg) was around 1.5% in children under 8 years of age, and 7.18% in the nationwide population between 1 and 59 years of age [2]. HBV has become the most important cause of chronic hepatitis and end-stage liver disease in China [2]. Treatment of chronic hepatitis B (CHB) with peginterferon has been reported in several independent studies, mainly of Caucasian patients. These studies suggest a more promising result using peginterferon than conventional interferon or lamivudine [3-6]. Peginterferon and nucleoside/nucleotide analogues are currently approved first-line treatments of chronic HBV infection and have been for a number of years [7,8]. However, this regimen is followed by some adverse effects, and large numbers of patients are not suitable candidates for treatment for a variety of reasons. The virological response achieved in peginterferon-treated CHB patients also needs to be improved. Complementary and alternative medicine (CAM) is therefore popular in the West. In 2007, almost 4 out of 10 adults surveyed in the United States (US) reported using CAM, whereas 42% used CAM in 1997 [9,10]. The widespread use of CAM is emphasized among people with chronic diseases, including CHB and chronic hepatitis C [11]. 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 systems, especially in China and some areas of Asia. Adverse reactions to Chinese herbs are rare and negligible when compared to those commonly produced by pharmaceutical drugs [9-14]. Interferon plus Chinese herbs is associated with higher sustained virological response than interferon alone in chronic hepatitis C and B [12-14]. Whether Chinese herbs can improve virological response compared to that yielded by peginterferon alone in CHB patients remains unclear. In recent years, a number of clinical trials have compared the efficacy and adverse effects of peginterferon therapies with peginterferon plus Chinese herbal therapies for the treatment of CHB. The aim of this study was to assess the evidence from these randomized clinical trials (RCTs) for the efficacy of peginterferon therapies compared with peginterferon plus Chinese herbal therapies.

Methodology

Eligibility criteria

The meta-analysis protocol used in this study was designed by Dr. Sihai Zhao. The included RCT studies were designed to compare the therapeutic effects of peginterferon therapies with peginterferon plus Chinese herbal therapies in hepatitis B e antigen (HBeAg)-positive CHB patients; patients co-infected with HCV and/or HIV were excluded. Only studies with patients who had been treated for at least 24 weeks were included. There were no language criteria for the included studies; publications could be written in any language. Finally, the studies had to include outcome measures (HBeAg seroconversion rates, serum HBeAg clearance rate, serum HBV DNA clearance rate, and ALT normalization rate). Reports of duplicated studies were excluded by examining the author list, parent institution, sample size, and results.

Outcome measures

HBeAg seroconversion rate, serum HBeAg clearance rate, serum HBV DNA clearance rate, and ALT normalization rate were used as the main outcome measures to assess the effects of peginterferon therapies with peginterferon plus Chinese herbal therapies. Serum HBeAg clearance or HBV DNA clearance was defined as reductions in HBeAg or HBV DNA to undetectable levels.

Information sources and searches

A search of the literature was conducted for studies that reported the therapeutic effects of peginterferon with or without Chinese herbal medicine therapies in CHB patients on 10 August 2014. 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 published in the field of antiviral therapy for CHB. The keywords used in literature searches included the following: chronic hepatitis B, hepatitis B virus, HBV, Chinese herbal therapy, Chinese traditional medicine, Chinese traditional drugs, herbs, peginterferon, pegylated interferon, HBeAg-positive, treatment, and trial.

Study selection and data collection

Two authors (Daxin Cheng and Liang Bai) independently screened titles and abstracts for potential eligibility and the full texts for final eligibility. The data were extracted 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 the age range and gender; the type of peginterferon (α-2a or α-2b); the doses of Chinese herbs and peginterferon; HBeAg seroconversion; viral suppression at the end of treatment and follow-up; the improvement of liver fibrosis related biomarkers; adverse effects; withdrawal rate; and reason for withdrawal.

Assessment of study quality

Two authors (Daxin Cheng and Enqi 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 treatment stopping.

Synthesis of results

The measure of association used in this meta-analysis was the odds ratio (OR) with a 95% confidence interval (CI). The summary OR with the 95% CI was calculated by Revman version 5.0 software using the random or fixed-effect 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. For continuous outcomes, a statistically significant result was assumed when the 95% CI did not include zero. Heterogeneity was explored using a Chi-square 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 616 studies, 8 of which matched the selection criteria (all in Chinese) [15-22]. All studies were designed as two-group RCTs to compare peginterferon plus Chinese herbal therapies with peginterferon therapies. There was unanimous agreement between the two authors regarding the selection of relevant articles (Sihai Zhao and Yonglie Chu).

Clinical trial characteristics

The eight RCTs included 624 patients. Seven RCTs that were included were published as full-length articles, and one was an unpublished master's thesis. The patients included in the eight trials were randomly assigned to accept peginterferon plus Chinese herbal therapies or peginterferon therapies alone.

Figure 1. Analysis of search results

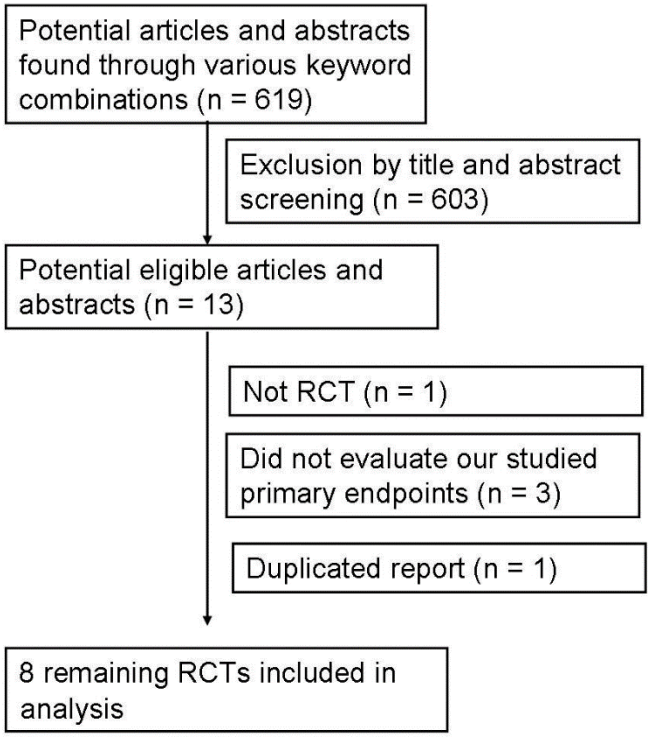
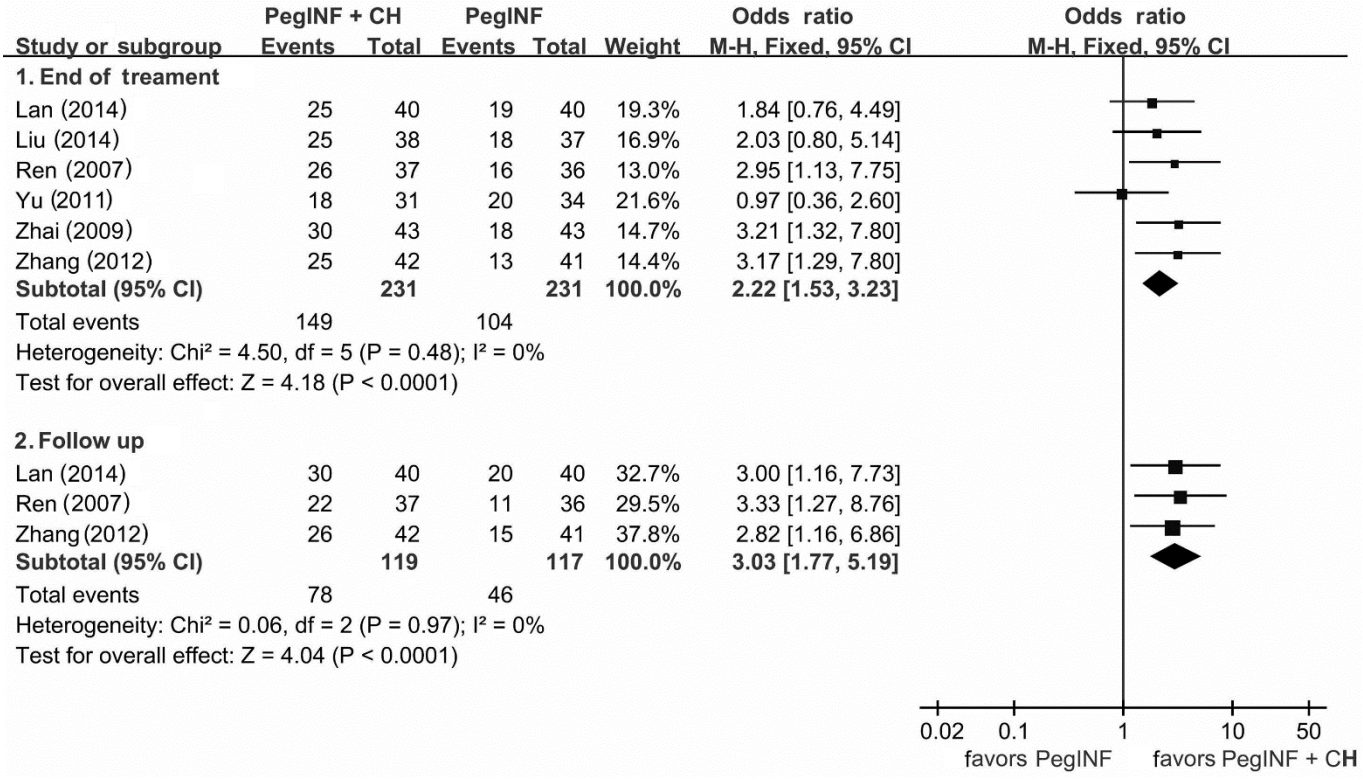


Figure 2. Serum HBV DNA clearance rates



PegINF: peginterferon; CH: Chinese herbs; CI: confidence interval; Test for heterogeneity: Chi-square statistic with its degrees of freedom (d.f.) and p value; Inconsistency among results: I^2 test for overall effect; Z statistic with p value

Of the 624 patients, 314 underwent therapy with peginterferon plus Chinese herbs, and 310 patients underwent therapy with peginterferon alone. All studies were single-center trials. The baseline characteristics of the included trials are summarized in Table 1. Information on the methodological quality was incomplete in the majority of eligible RCTs. The methodological quality of all eligible RCTs was not high.

Serum HBV DNA clearance rates

In this study, the combined serum HBV DNA clearance rate in the peginterferon plus Chinese herbs treatment group was higher than that in the peginterferon group at the end of the treatment and follow-up (end of treatment: 64.5% vs. 45.0%, OR: 2.22, 95% CI: 1.53–3.23, $p < 0.05$; follow-up: 65.5% vs. 39.3%, OR: 3.03, 95% CI: 1.77–5.19, $p < 0.05$) (Figure 2).

Serum HBeAg clearance rates

Serum HBeAg clearance rates were also analyzed in this study. Higher serum HBeAg clearance rates were obtained in patients treated with peginterferon plus Chinese herbs than in patients treated with peginterferon alone at the end of the treatment and follow-up (end of the treatment: 47.4% vs. 33.5%, OR: 1.83, 95% CI: 1.24–2.68, $p < 0.05$; follow-up: 57.0% vs. 33.8%, OR: 2.60, 95% CI: 1.36–4.97, $p < 0.05$) (Figure 3).

HBeAg seroconversion rates

HBeAg seroconversion rates were reported in five trials. The meta-analysis results showed that the HBeAg seroconversion rates were significantly greater in patients treated with peginterferon plus Chinese herbs than in patients treated with peginterferon alone at the end of the treatment (39.2% vs. 23.1%, OR: 2.18, 95% CI: 1.40–3.41, $p < 0.05$) (Figure 4).

Improvement of serum liver fibrosis related biomarkers

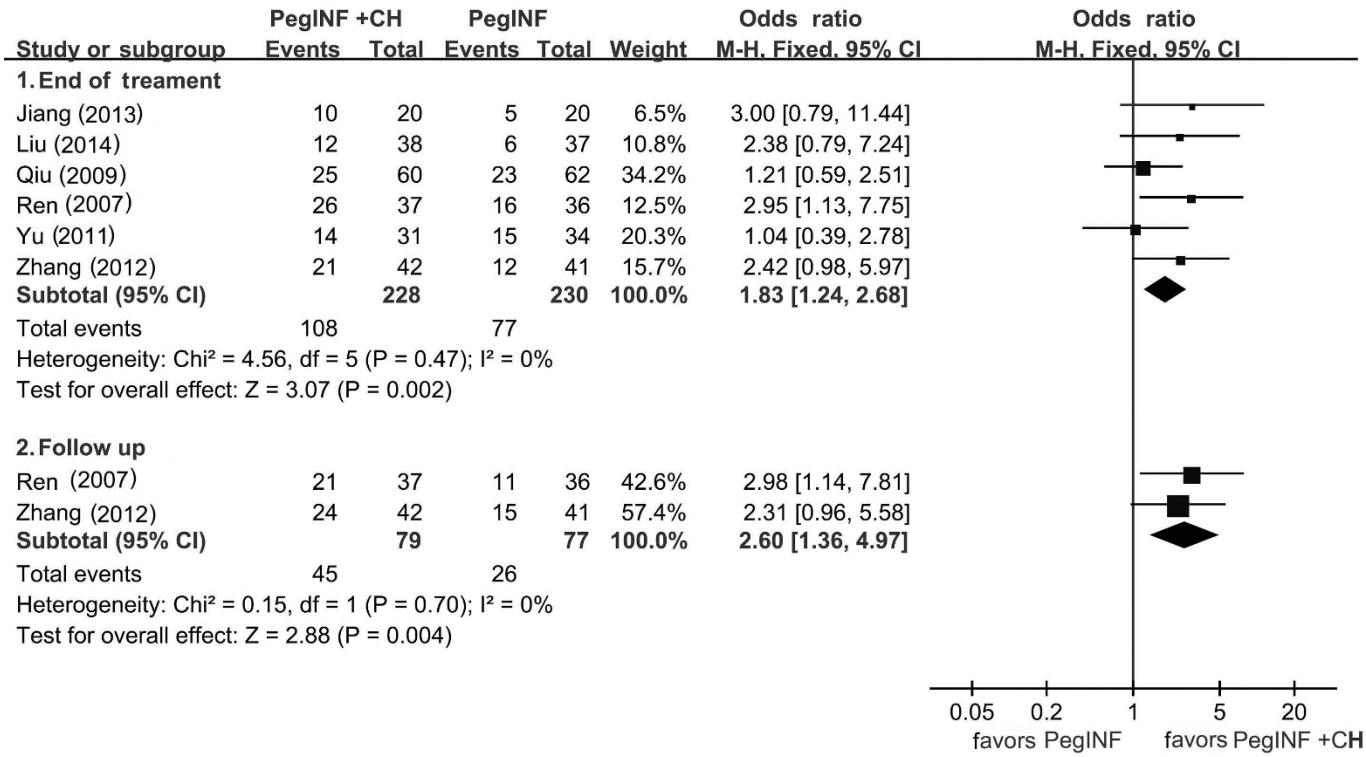
Three included trials in this study reported the data of two therapies on the improvement of serum liver fibrosis related biomarkers, which included hyaluronic acid, procollagen type III, type IV collagen, and lamina. Peginterferon plus Chinese herbal therapies were more effective than peginterferon alone therapies in the improvement of these biomarkers (Figure 5).

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

References	Sample size	Sex M/F	Mean age	HBV DNA (10^5 copies/mL)	Duration (weeks)	Follow up (weeks)	Control	Treatment
Jiang *et al*. [15]	20 20	18/2 18/2	29.0 ± 5.7 27.2 ± 5.7	252.64 ± 232.74* 190.10 ± 201.44*	24	0	PegIFN α-2b (1.0μg/kg/W)	Peginterferon α-2b (1.0μg/kg/W); Chinese medicinal formula (Taizishen 15 g, Chaobaishu 10 g, Huangmiao 15g, Cuchaihu 6g, Chuipengcao 30g, Yinchen 20g, Kushen 10g, Shengma 20g, Gegen 20g, Danshen 10g, Chaomaiya 15g; one dose daily)
Lan *et al*. [16]	40 40	34/6 35/5	33.9 ± 12.1 34.6 ± 10.1	-	48	24	PegIFN α-2a (135μg/W)	Peginterferon α-2a (135μg/W); Chinese medicinal formula (Fuling, Lingzhi, Shanyao, Gouqi, Duzhong, Zexie, Shudi; one dose daily)
Liu *et al*. [17]	37 38	48/27	27.2 ± 5.9	≥ 1	24	0	PegIFN α-2a (180μg/W)	Peginterferon α-2a (180μg/W); Liuweiwuling tablet (Wyweizi, Nvzhenzi, Lianqiao, Jumaicai, Lingzhibaozifen,Ezhu; 2.0g, t.i.d)
Qiu *et al*. [18]	62 60	54/8 52/8	33.1 ± 8.4 32.4 ± 7.6	> 1	48	0	PegIFN α-2a (180μg/W)	Peginterferon α-2a (180μg/W); Chinese medicinal formula (Yexiazhu 30g, Yinchen 30g, Zhizi 15g, Dahuangmiao 10g, Fuling 15g, Chishao 15g, Chenqiancao 15g, Yujin 15g, Huzhang 15g, Houpu 15g, Sharen 10g, Zhike 15g; one dose daily for 24 weeks)
Ren *et al*. [19]	36 37	28/8 32/5	35.7 ± 10.6 37.4 ± 11.5	6.4 ± 2.7* 6.1 ± 2.3*	24	24	PegIFN α-2a (180μg/W)	Peginterferon α-2a (180μg/W); Oxymatrine capsule (600 mg/day, p.o.)
Yu *et al*. [20]	31 34	51/14	20 ~ 50	> 1	48	0	PegIFN α-2a (180μg/W)	Peginterferon α-2a (180μg/W); Dahuang Zhechong pill (9g/day, p.o.)
Zhai *et al*. [21]	43 43	34/9 32/11	20 ~ 50	> 1	24	0	PegIFN α-2a (180μg/W)	Peginterferon α-2a (180μg/W); Matrine injection (150 mg /day, I.v.gtt; for 4 months)
Zhang *et al*. [22]	41 42	-/-	36.7 ± 10.6 38.4 ± 11.5	> 1	24	24	PegIFNα-2a (180μg/W)	Peginterferon α-2a (180μg/W) FuZhengHuaYu capsule (9g/day, p.o.) #

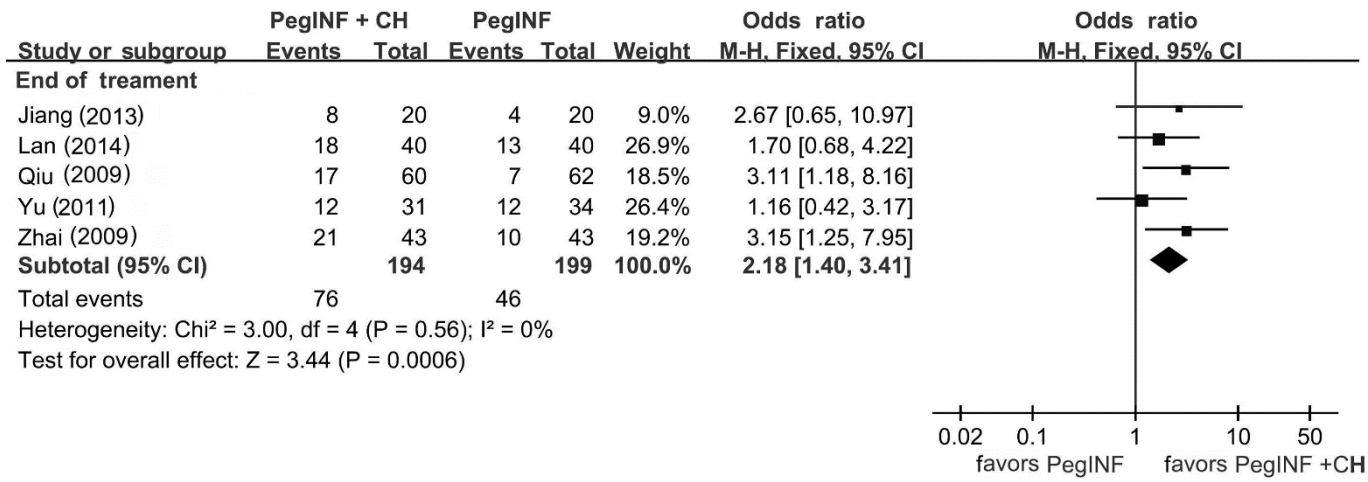
PegIFN: peginterferon; W: week; t.i.d.:Ter in die, three times a day; p.o: Per os, take medicine by oral; i.v.gtt.: injectio venosa gutta, intravenous drip; *HBV-DNA log10 copies/mL

Figure 3. Serum HBeAg clearance rates



PegINF: peginterferon; CH: Chinese herbs; CI: confidence interval; Test for heterogeneity: Chi-square statistic with its degrees of freedom (d.f.) and p value; Inconsistency among results: I^2 test for overall effect; Z statistic with p value

Figure 4. HBeAg seroconversion rates



PegINF: peginterferon; CH: Chinese herbs; CI: confidence interval; Test for heterogeneity: Chi-square statistic with its degrees of freedom (d.f.) and p value; Inconsistency among results: I^2 test for overall effect; Z statistic with p value

Serum ALT normalization

Analysis of combined data from the included studies of ALT normalization was also performed to compare the effect of peginterferon plus Chinese herbal therapies versus peginterferon alone therapies. Two studies presented the data as serum ALT normalization [19,22]. Another two studies presented the data of serum ALT levels as mean ± SD normalization [15,21]. The combined therapies achieved significantly higher serum ALT level reduction in Ren's [19] and Zhai's [21] studies. However, the differences were not significant in the remaining two studies [15,22].

Safety profile evaluation

The most frequently reported adverse events included pyrexia, myalgia, fatigue, and headache. There was no death nor liver decompensation associated with the treatment. The differences of overall adverse events or intercurrent illnesses reported in the included trials were not significant between patients treated with peginterferon plus Chinese herbal therapies and peginterferon alone therapies except Qiu *et al*.'s study [17]. In this study, the incidence rate of adverse events was lower in patients treated with peginterferon plus Chinese herbs (78% vs. 97.4%).

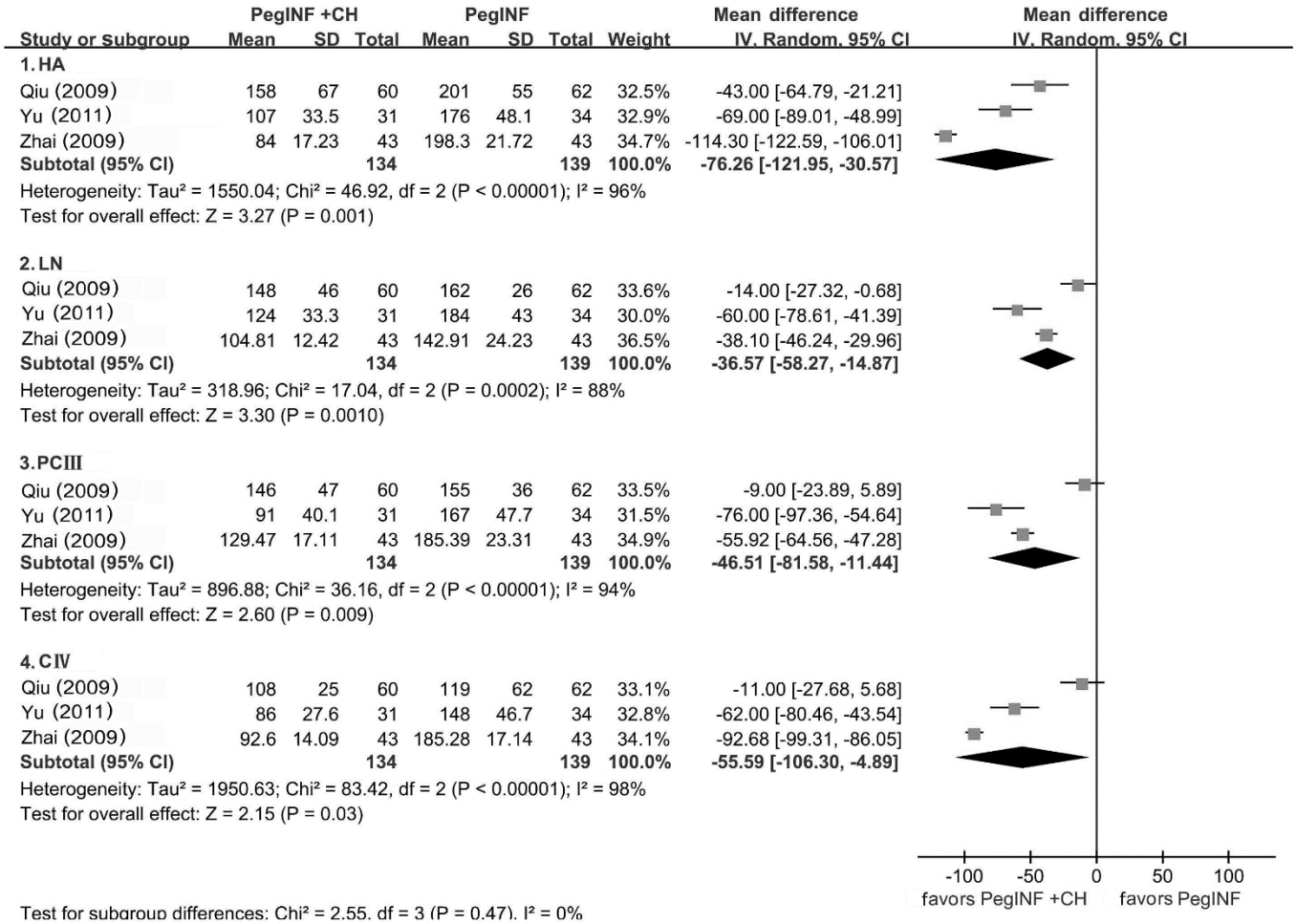
Publication bias

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 these clinical trials seemed reasonable and yielded fairly consistent results. However, publication bias could not be completely avoided because of the low methodological quality.

Discussion

Today, CHB is an unsolved medical problem and has become a serious worldwide public health problem,

Figure 5. Serum liver fibrosis related biomarkers



PegINF: peginterferon; CH: Chinese herbs; CI: confidence interval; Test for heterogeneity: Chi-square statistic with its degrees of freedom (d.f.) and p value; Inconsistency among results: I^2 test for overall effect; Z statistic with p value

both in developed and developing countries. However, there is no specific treatment for hepatitis B, a serious and widely epidemic disease. Liver failure due to CHB, especially HBeAg-positive CHB, is one of the unsolved medical problems and results in a significant number of deaths in China [2]. Therefore, treatment strategies for hepatitis B patients are urgently needed. Because of antiviral properties and immune regulation for viral hepatitis, peginterferon is widely used in the treatment of hepatitis B virus. Peginterferon achieved better effects than interferon did in the treatment of hepatitis B in previous studies [23]. Chinese herbs plus interferon have been associated with higher sustained virological response than interferon alone in chronic hepatitis C and B [12-14,24]. Chinese herbs have also been reported to improve the adverse effects of peginterferon or interferon in the treatment of chronic hepatitis [14,24]. Whether Chinese herbs can better improve virological response than peginterferon alone in HBeAg-positive CHB patients remains unclear. Therefore, we performed a new meta-analysis to compare the efficacy of peginterferon therapies with peginterferon plus Chinese herbal therapies in HBeAg-positive CHB patients.

In this study, we have summarized the available evidence from RCTs comparing peginterferon therapies with peginterferon plus Chinese herbal therapies in HBeAg-positive CHB patients. Our results suggest that combination therapies of peginterferon plus Chinese herbs may achieve significantly higher virological response than peginterferon therapies alone. Combination therapies of peginterferon plus Chinese herbs have shown higher HBeAg seroconversion rates, serum HBeAg clearance rate, serum HBV DNA clearance rate, ALT normalization rate, and improvement of serum liver-fibrosis related biomarkers than peginterferon therapies alone in HBeAg-positive CHB patients. Our previous study showed that the serum HBV DNA clearance rate of peginterferon was 44% [23]. In this study, the combined serum HBV DNA clearance rate in the peginterferon plus Chinese herbs treatment group was 64.7%, and it was higher than that in the peginterferon group (43.5%) and our previous study report. The similar benefit results of combination therapies were also achieved in higher HBeAg seroconversion rates, serum HBeAg clearance rate, and ALT normalization than had been reported in previous studies [3-6,23]. The incidences of adverse effects were lower in patients receiving combination therapies than in those receiving peginterferon therapies alone. Chinese herbs have also been revealed to have anti-fibrotic and anti-inflammatory activity in patients receiving peginterferon plus Chinese herbal therapies. Combination therapies of peginterferon plus Chinese herbs achieved more reduction in serum levels of hyaluronic acid, procollagen type III, type IV collagen, and lamina.

Current evidence suggests that combined therapies of peginterferon plus Chinese herbal therapies appear to be more efficacious than peginterferon monotherapy, and do not result in any additional safety problems in HBeAg-positive CHB patients. It is important to mention that there were limitations to the present meta-analysis. There is no epidemiological study with a sufficient number of cases that has shown an effect of HBV genotypes on the rate of HBV chronicity. We also did not analyze the role of HBV genotypes on the virological response of peginterferon plus Chinese herbal therapies. The quality of the included RCTs in this study was low because the full accounting of all randomized patients, follow-up, and blinding methods were not used. Although the main worldwide biomedical databases were searched to identify potential RCTs, publication bias could not be avoided completely.

Conclusions

In this study, we performed a meta-analysis of RCTs to compare peginterferon therapies with peginterferon plus Chinese herbal therapies in HBeAg-positive CHB patients. The current evidence suggests that peginterferon plus Chinese herbal therapies were associated with higher virological response than peginterferon alone in HBeAg-positive CHB patients.

Acknowledgements

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