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Peginterferon alpha versus other antiviral regimes for Chinese HBeAg-positive chronic hepatitis B patients

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ABSTRACT

Objective: To conduct a meta-analysis to determine the efficacy of peginterferon alpha (PEG-IFN α) therapy versus IFN α, adefovir dipivoxil (ADV) and entecavir (ETV) for HBeAg-positive chronic hepatitis B patients in China.

Methods: MEDLINE database and 3 main Chinese biomedical databases between 1966 and 2012 was retrieved. Two reviewers independently screened all reports to identify randomized controlled trials that evaluated PEG-IFN α therapy for the treatment of chronic hepatitis B in China.

Results: Fourteen trials met the eligibility criteria for this Meta analysis. PEG-IFN α therapy was more effective than IFN α therapy in achieving ALT normalization, serum HBV DNA clearance, HBeAg seroconversion, serum HBeAg clearance and fibrosis improvement in Chinese hepatitis B patients (P<0.05). PEG-IFN α was obviously superior to ETV in HBeAg seroconversion and serum HBeAg clearance (P<0.05), but the seroconversion rate was low. The combination therapy of PEG-IFN α and ADV was more effective than ADV monotherapy in ALT normalization, serum HBV DNA clearance and HBeAg seroconversion (P<0.05). PEG-IFN α showed no priority to other treatment regimes in HBsAg clearance.

Conclusion: Treatment with PEG-IFN α is safe and effective, and can be prescribed as first-line treatment options for chronic hepatitis B patients in China. Data are too limited to exclude a substantial benefit or harm of PEG-IFN α combination therapy for CHB patients in China.

KEY WORDS peginterferon alpha; Meta analysis; HBeAg-positive; chronic hepatitis B

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聚乙二醇干扰素α和其他抗乙肝病毒药物对中国HBeAg阳性慢性乙型肝炎患者的疗效对比

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[摘要]目的：通过Meta分析来评价聚乙二醇干扰素(peg interferon，PEG-IFN)α与IFN α、阿德福韦酯(adefovir dipivoxil，ADV)和恩替卡韦(entecavir，ETV)对中国HBeAg阳性慢性乙型肝炎患者的疗效。**方法：**计算机检索MEDLINE和3个主要的中文数据库(万方、维普和CNKI)，检索年限为1966年到2012年。由两名评价员对纳入的有关PEG-IFN α治疗中国HBeAg阳性慢性乙型肝炎患者的随机对照试验独立进行评价。**结果：**14个随机对照试验符合最终的纳入条件。Meta分析结果显示：在中国HBeAg阳性慢性乙型肝炎患者中，PEG-IFN α组的ALT复常率、HBV DNA阴转率、HBeAg血清转换率、HBeAg血浆清除率和肝纤维化的改善率均高于IFN α组，差异有统计学意义(P<0.05)。PEG-IFN α对HBeAg血清转换率和HBeAg血浆清除率明显优于ETV组，差异有统计学意义(P<0.05)，但总体的HBeAg血清转换率和HBeAg血浆清除率较低。PEG-IFN α与ADV的联合用药组ALT复常率、HBV DNA阴转率和HBeAg血清转换率高于ADV单药治疗组，差异有统计学意义(P<0.05)。PEG-IFN α对血浆HBsAg清除率和其他几种抗乙肝病毒药物相比无明显优势。**结论：**PEG-IFN α对中国HBeAg阳性慢性乙型肝炎患者疗效显著，可作为治疗中国HBeAg阳性慢性乙型肝炎的一线药物。而对PEG-IFN α的联合用药对中国HBeAg阳性慢性乙型肝炎患者的益处和危害尚缺乏足够的证据。

[关键词] PEG-IFN α；Meta分析；HBeAg阳性；慢性乙型肝炎

Hepatitis B virus (HBV) infection is a serious global public health problem[1]. In mainland China, liver failure due to chronic hepatitis B (CHB) is one of the unsolved medical problems and results in a significant number of deaths[2]. A nationwide survey showed that the prevalence of hepatitis B surface antigen (HBsAg) was around 1% in children under the age of 5 years, and 7.18% in the nationwide population at an age between 1 and 59 years[3]. HBV has become the most important cause of chronic hepatitis and end-stage liver disease in China. Therefore, treatment strategies for hepatitis B patients are urgently needed.

While the past two decades have brought major advances in the availability of treatments to help delay or prevent the HBV related outcomes, treatment of CHB remains a serious challenge. Although nucleotide/nucleoside analogs such as lamivudine (LAM) and adefovir dipivoxil (ADV) are well tolerated and effectively in DNA polymerase inhibition, sustained response after discontinuation of treatment is achieved in 55% of HBeAg-negative patients in adefovir dipivoxil and occurs in only 10%–15% of patients treated with LAM[4-5]. The recent availability of potent new nucleotide/nucleoside such as entecavir (ETV), tenofovir and telbuvidine do bring benefit to patients by providing highly effective HBV suppression, ALT normalization and improvement in liver histology. However, the HBsAg seroconversion is rarely observed when compared with interferon α (IFN α) and peg interferon alpha (PEG-IFN α) based treatment, and sustained, off-therapy response is more often followed by relapse[6].

Conventional IFN α is approved first-line treatments of chronic HBV infection for a number of years. IFN α acts mainly as immunomodulator and enhances the host cell-mediated immune response, enabling it to decrease viral loads and increase rates of HBeAg seroconversion to antibody against HBeAg. The disadvantages of conventional IFN α include contraindication in patients with decompensated liver disease, and clinically significant side effects. Treatment of CHB with PEG-IFN α has been reported in several independent studies. These studies suggest a more promising result treating PEG-IFN α than conventional interferon or lamivudine[7-10], and PEG-IFN α was recommended as first-line treatment regime for CHB.

However, the actual situation in mainland China is that the clinical acceptance of PEG-IFN α treatment is generally low for CHB patients for its high costs, which makes PEG-IFN α efficacy assessment more difficult in China[11], so the optimal choice for individual patients remains controversial. In recent years, several new clinical trials to compare the efficiency of PEG-IFN α treatment with other antiviral regimes in patients with hepatitis B in China were published. However, the

numbers of patients included in these clinical trials are too small to draw a clear conclusion. Therefore, we performed a Meta analysis of randomized control trials (RCTs) included relative large numbers patients by collecting data form MEDLINE database and three main Chinese biomedical databases to examine the beneficial effects of PEG-IFN α therapy in patients with hepatitis B in China. The aim of this report is to present a comparative analysis of the benefit and harms of PEG-IFN α based therapy for HBeAg-positive CHB infection and provide the basis for evidence-based decision making in clinical settings.

1 MATERIALS AND METHODS

1.1 Search strategy

National Library of Medicine (Medline, Bethesda, MD, USA) (1966–2012), China National Knowledge Infrastructure (CNKI, Beijing, China) (1979–2012), Wanfang Database (Wanfangdata Co., Ltd, Beijing, China) (1985–2012) and China Biomedical Database (CBM, Beijing, China) (1985–2012) were searched to identify RCTs published in the area of hepatitis B and antiviral therapy in China. The retrieval was finished in October 2012. The keywords used in literature searches included hepatitis B, HBV, peginterferon, pegylated interferon, PEG-IFN α, treatment and trial. In addition, a manual search based on reference lists from previous publications involving PEG-IFN α treatment was conducted.

1.2 Data extraction

The included studies were divided into different groups according to intervention treatments. Data were independently extracted by two authors (DENG Zhenzhen and WANG Chunjiang) from inclusion trials for quantitative analysis, and any disagreement was subsequently resolved by discussion. The quantitative data included study design, sample size, treatment regimens, therapy period and follow-up period, adverse effects, withdrawal rate and reason for withdrawal. Outcome variables were defined as virological response (HBV DNA clearance rates), serological response (seroconversion rates and clearance rates of HBeAg and HBsAg), biochemical response (ALT normalization rates) and histological response [the reduced rates of hyaluronic acid (HA), procollagen type III (PC-III), type IV collagen (IV-c), lamina (LN)] at the end of treatment and post-treatment.

1.3 Criteria for inclusion and exclusion

Inclusion criteria defined as follows i) study design: RCTs, no matter whether adopted blind method or not; ii) study population: HBeAg-positive CHB patients in China; iii) intervention: PEG-IFN α combined with nucleotide/nucleoside analogs therapy versus nucleotide/nucleoside analogs monotherapy, PEG-IFN α versus IFN or nucleotide/nucleoside analogs; iv) language of publication: English or Chinese.

The exclusion criteria were as follows i) study design: non-RCTs; ii) study population: non-adult population, women with pregnancy or lactation, patients received liver transplantation, patients co-infected with hepatitis C virus, hepatitis D virus or human immunodeficiency virus, patients with a history of alcohol or drug abuse, hepatocellular carcinoma, decompensated liver disease, serious medical or psychiatric illness; iii) intervention: concurrently using corticosteroid, immunosuppressive agents, other antiviral agents like ribavirin or Chinese herbal medicine; iv) republished studies.

1.4 Quality assessment

Jadad scale was used to assessment the quality of trials, Jadad score was evaluated by the adequacy of random assignment, double-blinding, and reporting of subjects withdraw or drop out [12].

1.5 Statistical analysis

Quantitative meta-analyses were performed to assess differences between groups. Statistical analysis was performed and the Forest plots were generated using "Review Manager" software (RevMan 5.0). The risk ratios (RR) were calculated along with their respective 95% confidence intervals (CI) and were presented for each study. Statistical heterogeneity between trials was evaluated by the chi-square (χ^2) and I square (I^2) tests, with significance being taken as $P<0.1$. $I^2>50\%$ were thought to be statistically significant heterogeneity. In the absence of statistically significant heterogeneity, the fixed-effect method was used to combine the results. When heterogeneity was confirmed ($P\leqslant 0.1$), the random-effect method was used. The overall effect was tested using Z scores, with significance set at $P<0.05$. Publication bias was assessed by funnel plots.

2 RESULTS

2.1 Clinical trial characteristics

Our computerized and manual keywords searches identified 892 articles, of which 860 were in vitro studies, studies unrelated to CHB, duplicate reports, or contained no primary data about effectiveness. Full texts were reviewed for the remaining 32 report. Of these trials,

fourteen were judged potentially eligible, RCT employing PEG-IFN α therapy for HBeAg-positive, chronic HBV infection in China. Of the eighteen excluded, eight were duplicate publications, four were not designed as RCT and another six were excluded because the interventions employed different ribavirin therapies. Overall, fourteen trials involving a total of 1274 patients were satisfied eligibility criteria for this meta-analysis. Among these trials, ten are comparison of PEG-IFN α and IFN α therapies[13-22], three are comparison of combination of PEG-IFN α and ADV with ADV monotherapy[23-25] and one is comparison of PEG-IFN α and ETV therapies[26]. Of these studies, two were high-quality（Jadad scores of 3–5)and the other twelve were low-quality（Jadad scores <3 respectively). All trials were performed in patients of Chinese original and were published as full publications. The characteristics of these included studies are summarized in the Table 1.

Table 1 Characteristics of the trials included in the Meta analysis

Study	Therapeutic regimen	Sample size	Dose	Therapy period/ week	Following period/ week	Primary endpoint	Jadad score
Sun[13] (2009)	PEG-IFN α-2a	25	180 μg/w	48	48	ALT normalization, HBV DNA clearance, HBeAg seroconversion, HBeAg clearance, HBsAg clearance	2
	IFN α-2a	21	500 MU/qod				
Li[14] (2010)	PEG-IFN α-2a	39	180 μg/w	48	24	ALT normalization, HBV DNA clearance, HBeAg seroconversion, HBeAg clearance, HBsAg clearance	2
	IFN α-2a	38	500 MU/qod				
Cui[15] (2006)	PEG-IFN α-2a	40	180 μg/w	48	48	ALT normalization, HBV DNA clearance, HBeAg seroconversion, HBeAg clearance, HBsAg clearance	3
	IFN α-2a	40	500 MU/qod				
Li[16] (2009)	PEG-IFN α-2a	40	180 μg/w	48	24	ALT normalization, HBV DNA clearance, HBeAg seroconversion, HBeAg clearance, HBsAg clearance	2
	IFN α-2a	40	500 MU/qod				
Yi[17] (2012)	PEG-IFN α-2a	42	180 μg/w	48	24	HBV DNA clearance, HBeAg seroconversion, HBsAg clearance, HBsAg clearance	2
	IFN α-2a	42	500 MU/qod				
Cheng[18] (2007)	PEG-IFN α-2a	27	180 μg/w	48	48	ALT normalization, HBV DNA clearance, HBeAg seroconversion, HBeAg clearance	2
	IFN α-2b	34	500 MU/qod				
Zhong[19] (2010)	PEG-IFN α-2a	22	180 μg/w	48	0	ALT normalization, HBV DNA clearance, HBeAg seroconversion, HBeAg clearance	2
	IFN α-2a	22	500 MU/qod				
Nie[20] (2008)	PEG-IFN α-2a	33	180 μg/w	48	48	ALT normalization, HBV DNA clearance, HBeAg seroconversion, HBeAg clearance	2
	IFN α-2a	33	300 MU/qod				
Zhao[21] (2006)	PEG-IFN α-2b	115	180 μg/w	24	24	ALT normalization, HBV DNA clearance, HBeAg seroconversion, HBeAg clearance	2
	IFN α-2b	115	300 MU/qod				
Gao[22] (2008)	PEG-IFN α-2a	30	180 μg/w	48	24	HBV DNA clearance, HBeAg clearance	2
	IFN α-2a	31	300 MU/qod				
Ao[23] (2010)	PEG-IFN α-2a	40	135 μg/w	48	48	ALT normalization, HBV DNA clearance, HBeAg seroconversion, HBsAg clearance	3
	ADV	40	10 mg/d				
	PEG-IFN α-2a+ADV	40	135 μg/w+ 10 mg/d				
Ding[24] (2011)	PEG-IFN α-2a	21	180 μg/w	48	0	ALT normalization, HBV DNA clearance, HBeAg seroconversion, HBsAg clearance	2
	ADV	22	10 mg/d				
	PEG-IFN α-2a+ADV	17	180 μg/w+ 10 mg/d				
Li[25] (2012)	PEG-IFNα-2b+ADV	82	180 μg/w+ 10 mg/d	48	48	ALT normalization, HBV DNA clearance, HBeAg seroconversion	2
	ADV	116	10 mg/d				
Chen[26] (2010)	PEG-IFN α-2a	34	180 μg/w	48	0	HBV DNA clearance, HBeAg seroconversion, HBsAg seroconversion, HBeAg clearance, HBsAg clearance	2
	ETV	33	0.5 mg/d				

2.2 Comparison of PEG-IFN α and IFN α therapy

2.2.1 ALT normalization rates

Our Meta analysis results showed that the ALT normalization rates were significant greater for patients treated with PEG-IFN α than for patients treated with IFN α at 24th, 48th week of the treatment [57% vs 38%, RR=1.44, 95% CI (1.22, 1.70), P<0.01; 75% vs 47%, RR=1.51, 95% CI (1.28, 1.79), P<0.01] and the 48th week of follow-up [57% vs 38%, RR=1.58, 95% CI (1.22, 2.09), P<0.01], but not in 24th week of follow-up [47% vs 36%, RR=1.46, 95% CI (0.93, 2.30), P=0.10]. The combination results of each time-point showed significant effectiveness of PEG-IFN α [RR=1.47, 95% CI (1.34, 1.62), P<0.01] (Figure 1). The random effect model was used for I^2>50% in the 24th week of follow-up.

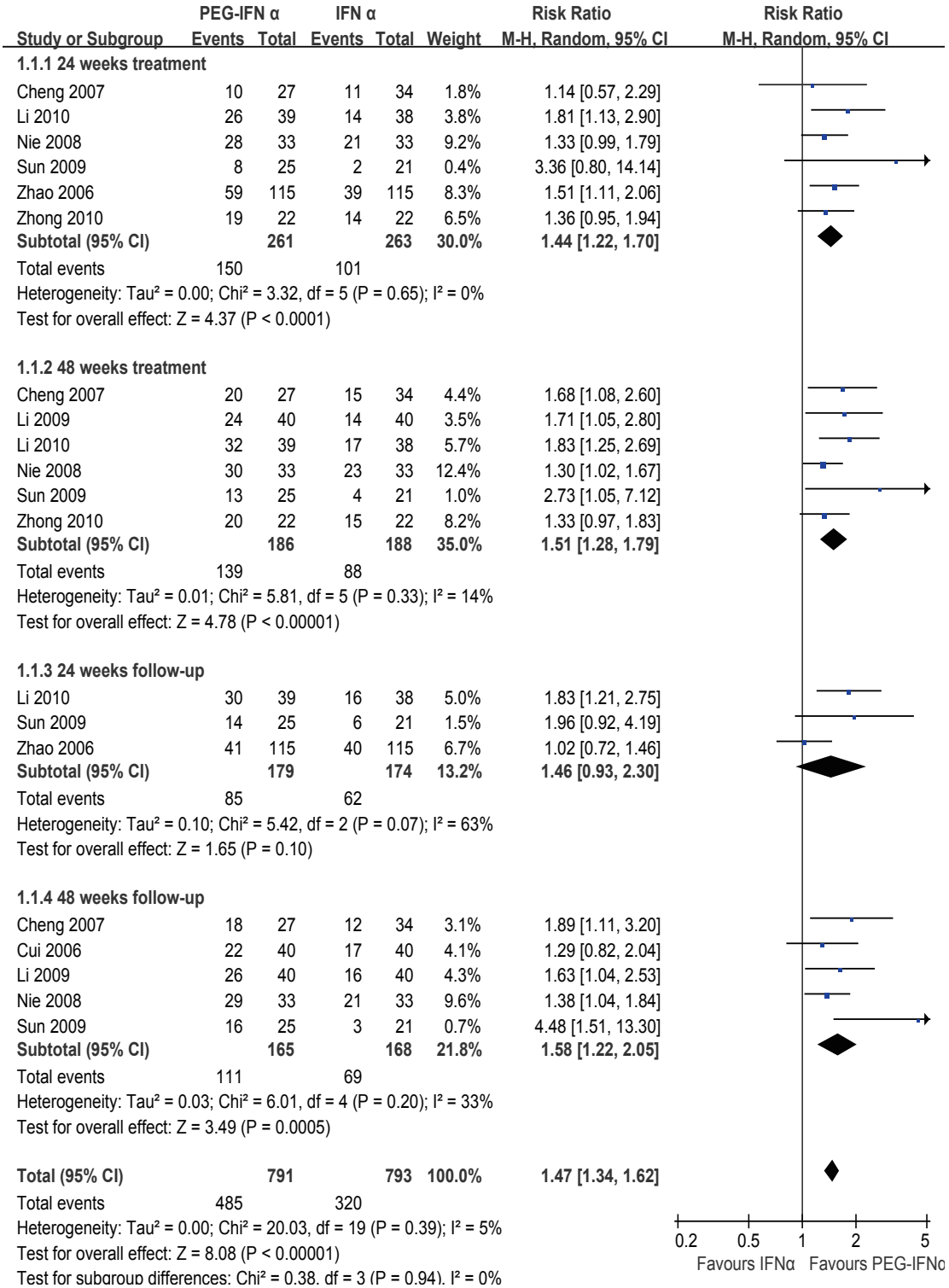

Figure 1 ALT normalization rates, subgroup analysis of PEG-IFN α vs IFN α in the treatment of Chinese hepatitis B patients.

2.2.2 HBV DNA clearance rates

Higher serum HBV DNA clearance rates were obtained in patients treated with PEG-IFN α than for patients treated with IFN α at the 24th, 48th week of the treatment [44% vs 31%, RR=1.48, 95% CI (1.13, 1.73), P<0.01; 62% vs 38%, RR=1.63, 95% CI (1.37, 1.94), P<0.01] and the 24th, 48th week of follow-up [45% vs 21%, RR=2.18, 95% CI (1.65, 2.88), P<0.01; 55% vs 33%, RR=1.68, 95% CI (1.30, 2.17), P<0.01]. The combination results of each time-point showed significant effectiveness of PEG-IFN α [RR=1.66, 95% CI (1.49, 1.85), P<0.01] (Figure 2). Fix-effect model was adopted for I^2<50% in all the subgroups.

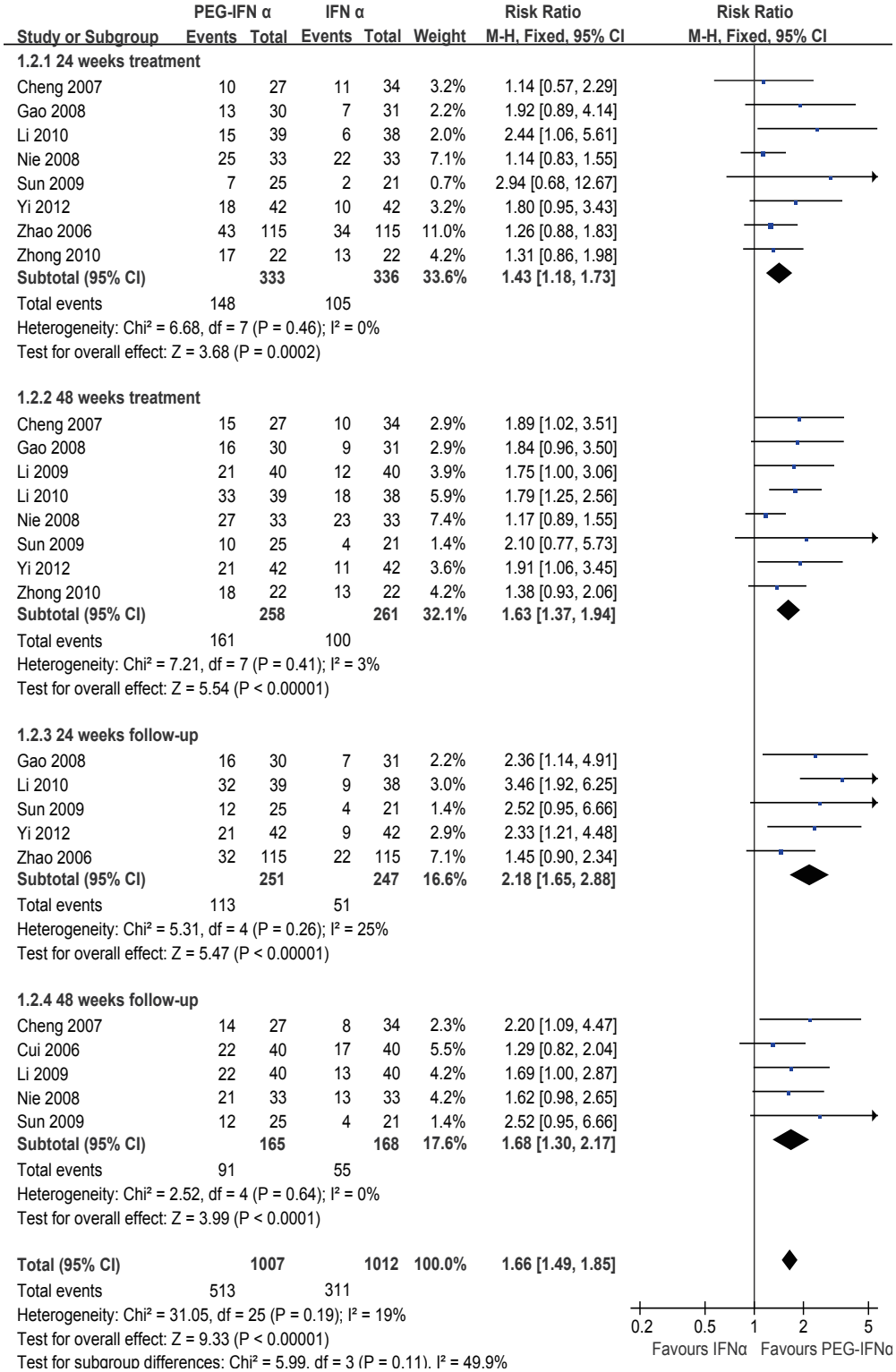

Figure 2 HBV DNA clearance rates, subgroup analysis of PEG-IFN α vs IFN α in the treatment of Chinese hepatitis B patients.

2.2.3 HBeAg seroconversion rates

HBeAg seroconversion rates were reported in eight trials. The combined data of HBeAg seroconversion rates in the PEG-IFN α treatment group were significant higher than that in the IFN α group at the 24th, 48th week of the treatment [30% vs 17%, RR=1.68, 95% CI (1.22, 2.31), P<0.01; 44% vs 25%, RR=1.77, 95% CI (1.32, 2.38), P<0.01] and the 24th, 48th week of follow-up [28% vs 16%, RR=1.72, 95% CI (1.15, 2.56), P<0.01; 44% vs 24%, RR=1.83, 95% CI (1.33, 2.58), P<0.01]. The combination results of each time-point showed significant effectiveness of PEG-IFN α [RR=1.75, 95% CI (1.49, 2.06), P<0.01] (Figure 3). Fix-effect model was adopted for I^2<50% in all the subgroups.

2.2.4 HBeAg clearance rates

Serum HBeAg clearance rates were also been analysis in this study. Higher serum HBeAg clearance rates were obtained in patients treated with PEG-IFN α than in patients treated with IFN α at the 24th, 48th week of the treatment [33% vs 21%, RR=1.57, 95% CI (1.20, 2.06), P<0.01; 53% vs 28%, RR=1.88, 95% CI (1.47, 2.41), P<0.01] and the 24th, 48th week of follow-up [34% vs 19%, RR=1.82, 95% CI (1.30, 2.55), P<0.01; 52% vs 27%, RR=1.93, 95% CI (1.44, 2.58), P<0.01]. The combination results of each time-point showed significant effectiveness of PEG-IFN α [RR=1.78, 95% CI (1.55, 2.05), P<0.01] (Figure 4). Fix-effect model was adopted for I^2<50% in all the subgroups.

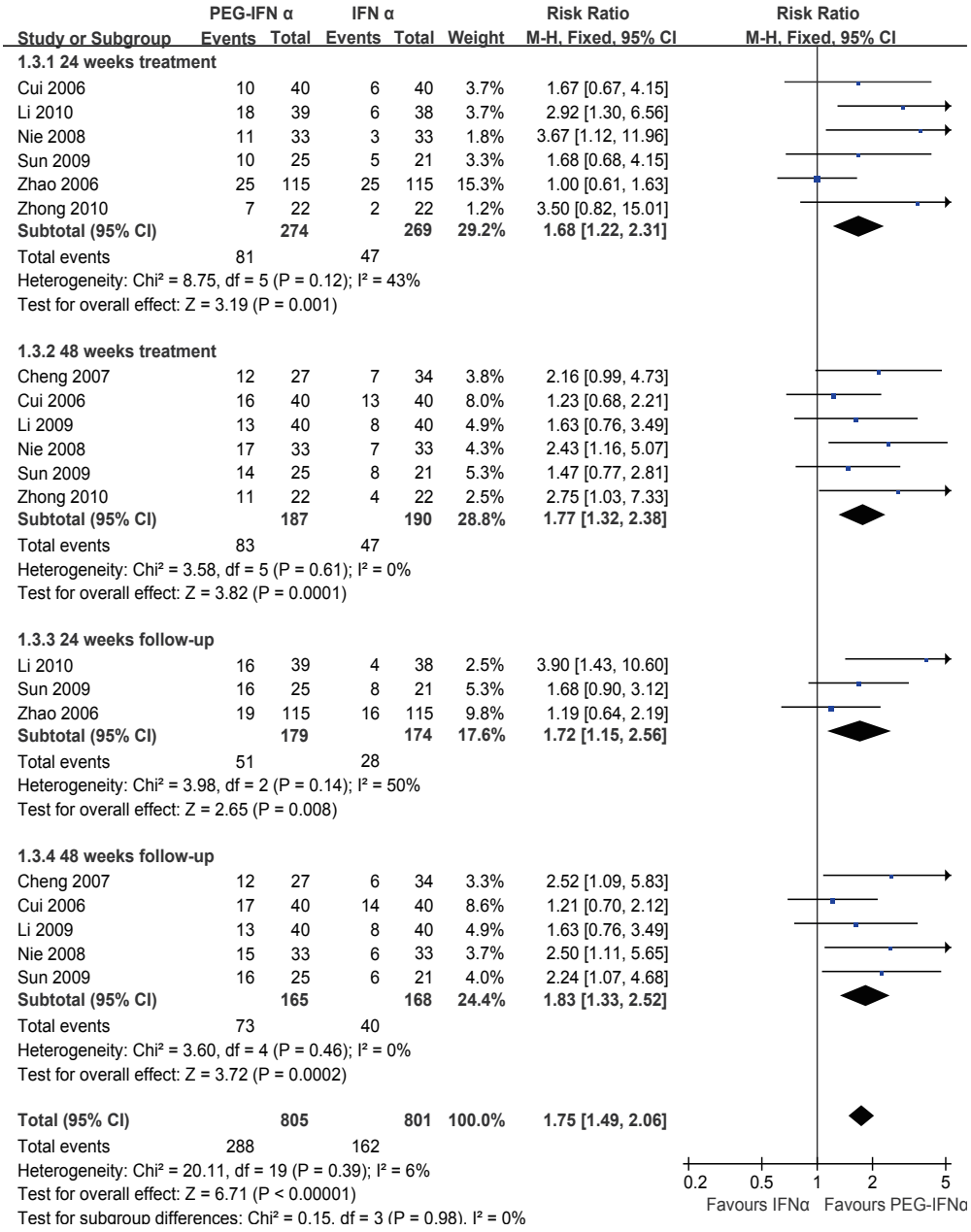

Figure 3 HBeAg seroconversion rates, subgroup analysis of PEG-IFN α vs IFN α in the treatment of Chinese hepatitis B patients.

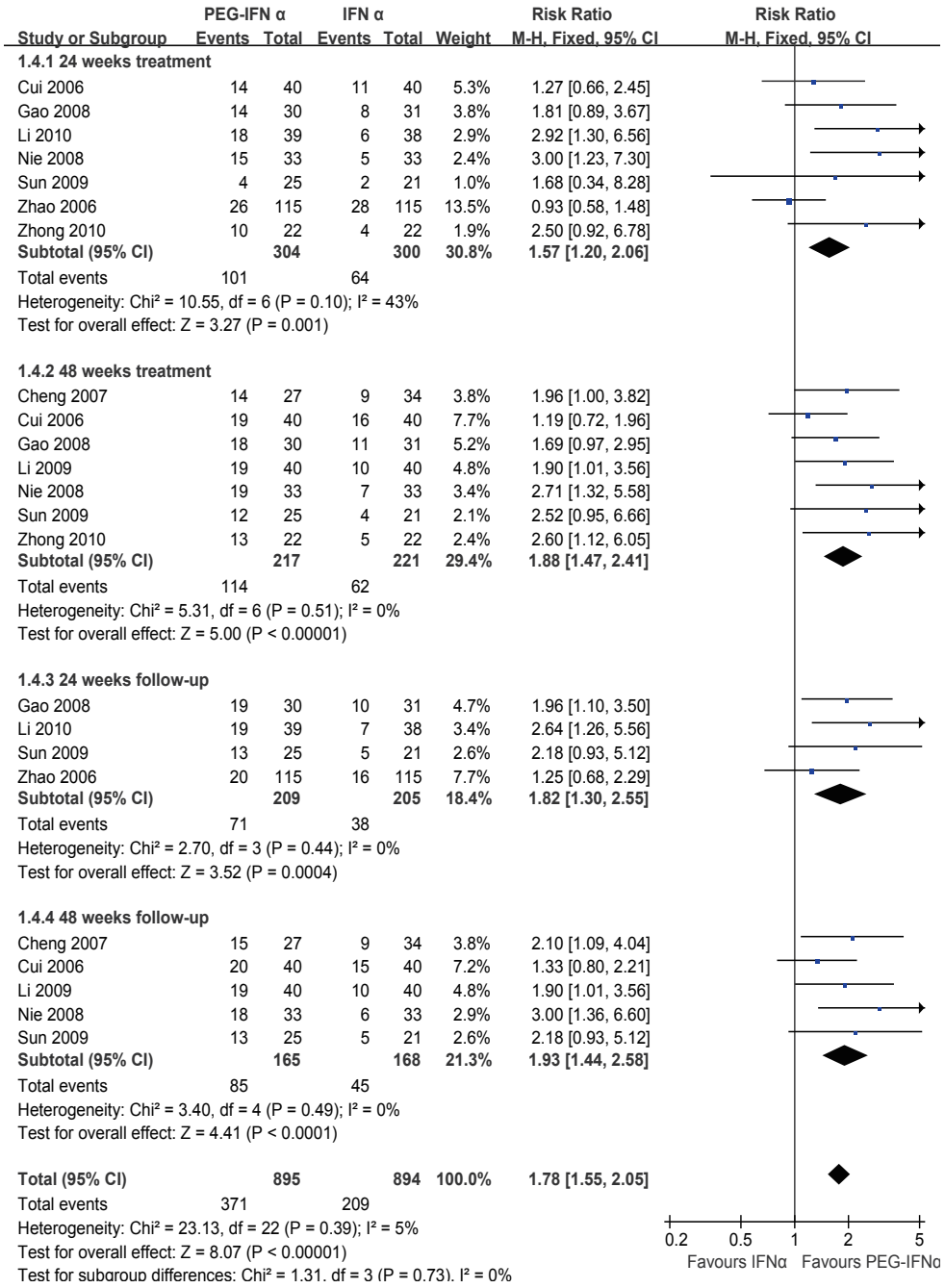

Figure 4 HBeAg clearance rates, subgroup analysis of PEG-IFN α vs IFN α in the treatment of Chinese hepatitis B patients.

2.2.5 HBsAg clearance rates

Analysis of combined data from included studies for HBsAg clearance rate was performed to compare the effect of PEG-IFN α therapy vs IFN α therapy. The combined HBsAg clearance rate was 3.8% in PEG-IFN α treatment group and 1.1% in the IFN α treatment group, the difference between the two groups did not show statistic significance [RR=2.33, 95% CI (0.83, 6.56), P=0.11] (Figure 5). Fix-effect model was adopted for I^2=0.

2.2.6 Hepatic fibrosis improvement rates

Two included trials in this study reported the data of PEG-IFN α therapy vs IFN α therapy on the improvement of liver fibrosis related biomarkers, included the reduced rate of HA, PC III, IV-c and LN. PEG-IFN α therapy was more effective than IFN α therapy in the improvement of these biomarkers.

2.2.7 Safety profile

The frequencies and severity of adverse events were similar in both treatment groups. Common side-effects included pyrexia, myalgia, fatigue, descended body weight, baldness, descended body weight, baldness, headache and so on. All the adverse events were reversible after treatment was stopped.

2.3 Comparison of PEG-IFN α + ADV with ADV monotherapy

2.3.1 ALT normalization rates

In comparison of the ADV monotherapy, the combination therapy of PEG-IFN α and ADV led to higher ALT normalization rates during 48th week of follow-up [75% vs 62%, RR=1.24, 95% CI (1.07, 1.45), P<0.01], but not in 24th and 48th week of treatment [58% vs 56%, RR=1.03, 95% CI (0.75, 1.40), P=0.86; 70% vs 63%, RR=1.12, 95% CI (0.87, 1.44), P=0.38]. The combination results of each time-point showed significant effectiveness of the combination therapy [RR=1.17, 95% CI (1.03, 1.32), P=0.01] (Figure 6). Fix-effect model was adopted for I^2=0 in all the subgroups.

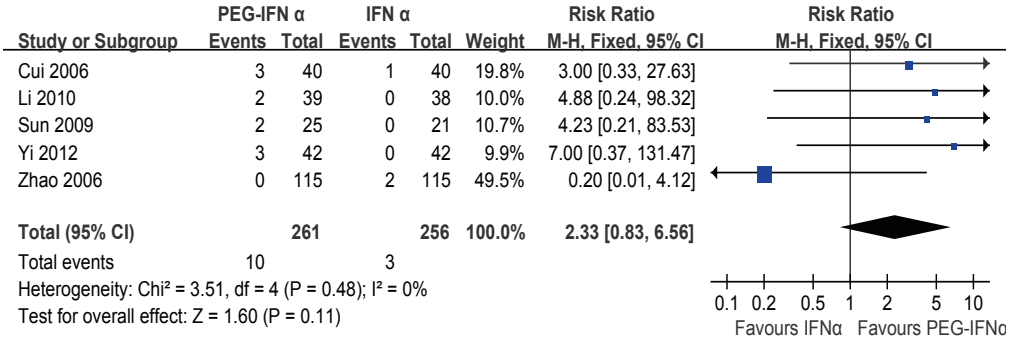

Figure 5 HBsAg clearance rates, subgroup analysis of PEG-IFN α vs IFN α in the treatment of Chinese hepatitis B patients.

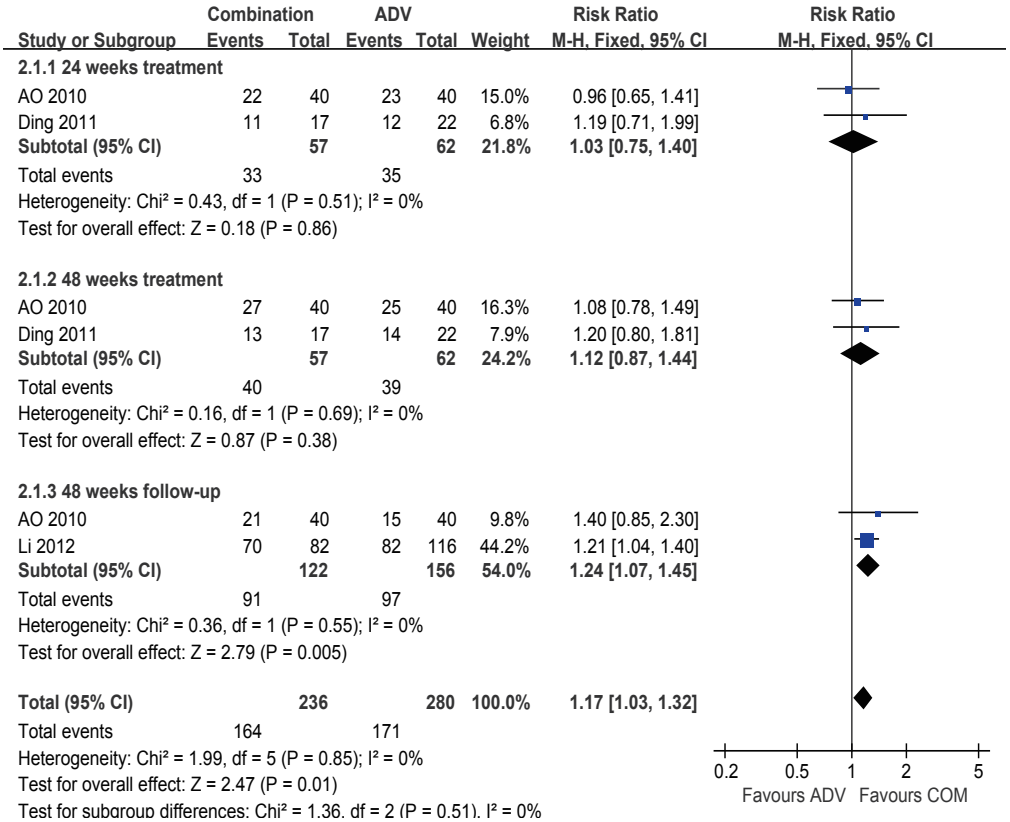

Figure 6 ALT normalization rates, subgroup analysis of PEG-IFN α+ADV vs ADV in the treatment of Chinese hepatitis B patients.

2.3.2 HBV DNA clearance rates

Higher serum HBV DNA clearance rates were obtained in patients treated with combination group than for patients treated with ADV at the 48th week of the treatment [63% vs 42%, RR=1.56, 95% CI (1.11, 2.19), *P*=0.01]. The combination group was equivalent to ADV monotherapy in the 24th week of treatment and 48th week of follow-up [51% vs 37%, RR=1.43, 95% CI (0.96, 2.13), *P*=0.08; 77% vs 58%, RR=1.77, 95% CI (0.73, 4.28), *P*=0.20]. The combination results of each time-point showed significant effectiveness of the combination therapy [RR=1.41, 95% CI (1.20, 1.66), *P*<0.01] (Figure 7). Random effect model was used for I^2>50% in the 48th week of follow-up.

2.3.3 HBeAg seroconversion rates

HBeAg seroconversion rates were reported in three trials. The combined data of HBeAg seroconversion rates in the combination treatment group were significant higher than that in the ADV monotherapy group at the 24th, 48th week of treatment [28% vs 11%, RR=2.35, 95% CI (1.06, 5.21), *P*=0.04] and the 48th week of follow-up [40% vs 16%, RR=2.49, 95% CI (1.67, 3.71), *P*<0.01; 45% vs 21%, RR=2.17, 95% CI (1.51, 3.12), *P*<0.01]. The combination results of each time-point showed significant effectiveness of the combination therapy [RR=2.32, 95% CI (1.80, 2.99), *P*<0.01] (Figure 8). Fix-effect model was adopted for I^2=0 in all the subgroups.

2.3.4 HBsAg clearance rates

Analysis of combined data from included studies for HBsAg clearance rate was also performed to compare the effect of combination therapy vs ADV monotherapy. The combined HBsAg clearance rate was 5.3% in combination treatment group and 0 in the ADV treatment group, the difference between the two groups did not show statistic significance [RR=4.58, 95% CI (0.54, 38.77), *P*=0.16] (Figure 9). Fix-effect model was adopted for I^2=0.

2.3.5 Safety profile

Of the three included trials, only two of them reported adverse events. The most frequently reported adverse events included pyrexia, myalgia, fatigue, and headache were more often happened in the combination group than in the ADV monotherapy. There was no death associated with the treatment, or liver decompensation. All the adverse events were reversible after treatment was stopped.

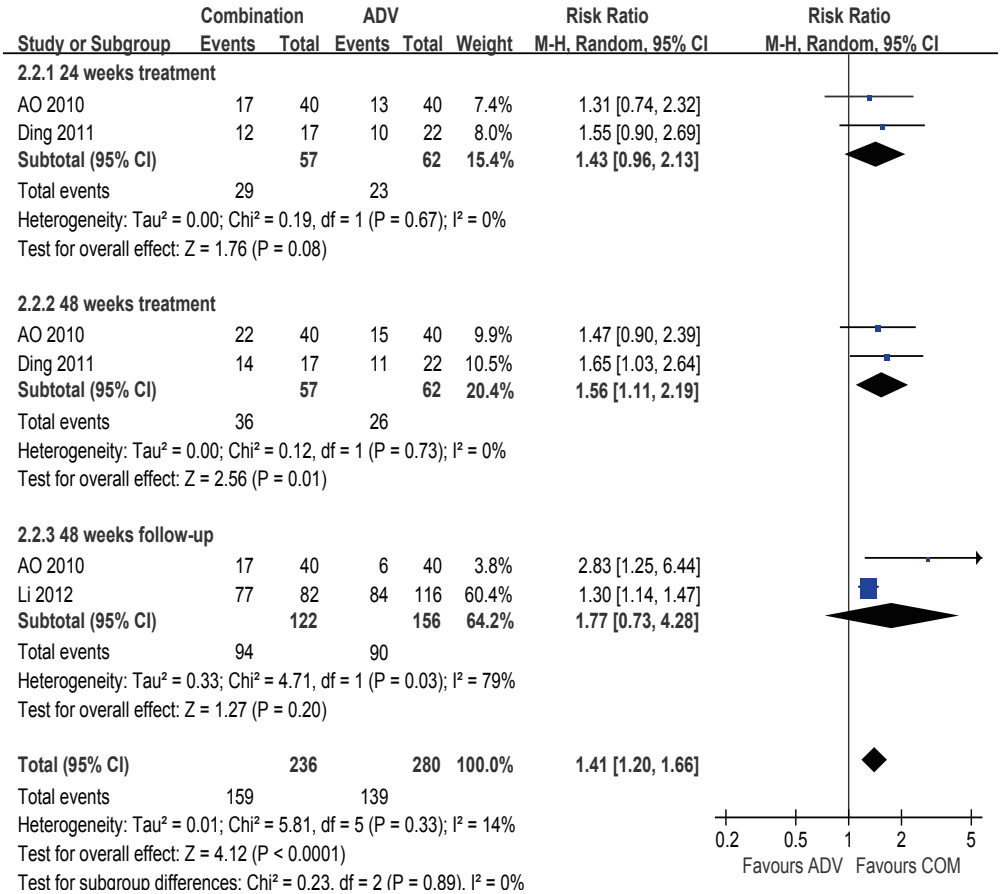

Figure 7 HBV DNA clearance rates, subgroup analysis of PEG-IFN α+ADV vs ADV in the treatment of Chinese hepatitis B patients.

2.4 Comparison of PEG-IFN α and ETV therapy

Comparison of PEG-IFN α and ETV therapy were reported in one trial. The meta-analysis results showed that the HBeAg seroconversion rates and serum HBeAg clearance rates were significant greater for patients treated with PEG-IFN α than for patients treated with ETV [41% vs 12%, RR=3.40, 95% CI (1.25, 9.26), *P*=0.02; 41% vs15%, RR=2.72, 95% CI (1.10, 6.70), *P*=0.03]. PEG-IFN α therapy was equivalent to ETV therapy in the serum HBV DNA clearance rates [65% vs 70%, RR=0.93, 95% CI (0.66, 1.30), *P*=0.66], serum HBsAg clearance [12% vs 3%, RR=3.88, 95% CI (0.46, 32.94), *P*=0.21] and HBsAg seroconversion [12% vs 0, RR=10.54, 95% CI (0.59, 189.08), *P*=0.11] (Figure 10). Heterogeneity was not applicable for only one case was selected.

No significant difference was found of the histological improvement between the two groups. Adverse events happened in 31 patients in PEG-IFN α treatment group, no adverse events were found in the ETV treatment group. All the adverse events were reversible after treatment was stopped.

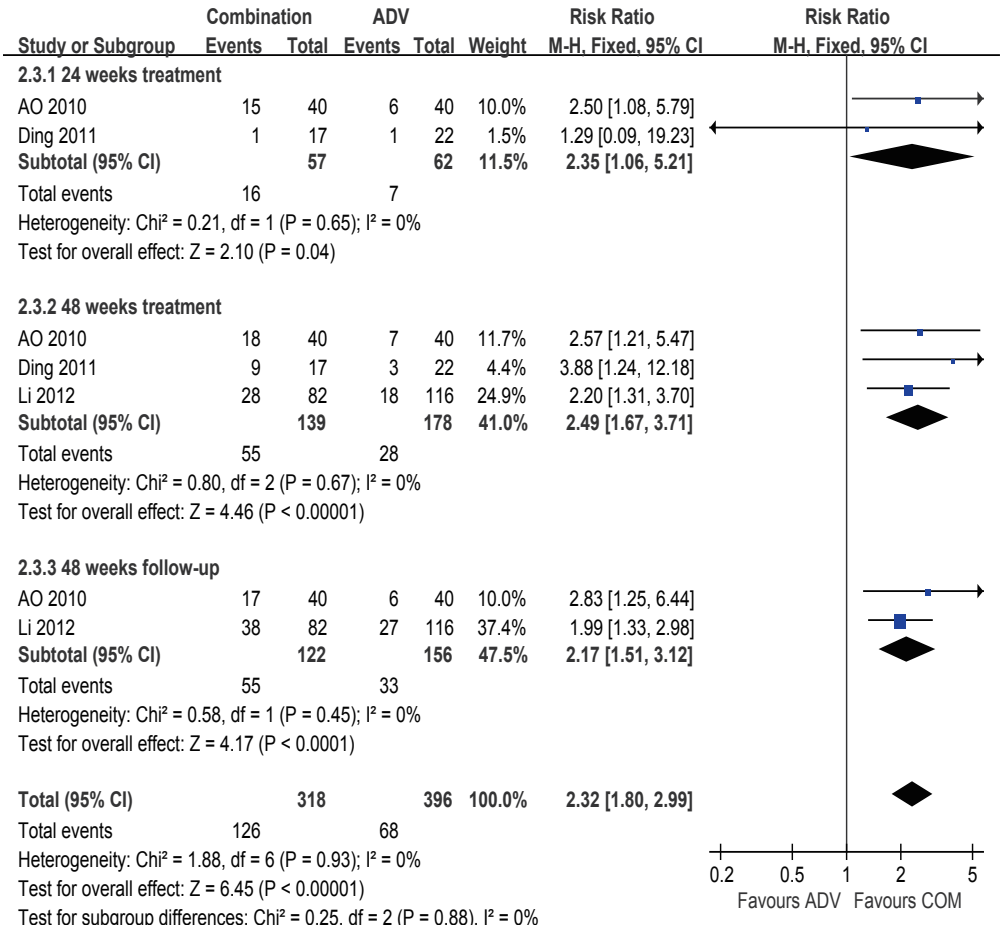

Figure 8 HBeAg seroconversion rates, subgroup analysis of PEG-IFN α+ADV vs ADV in the treatment of Chinese hepatitis B patients.

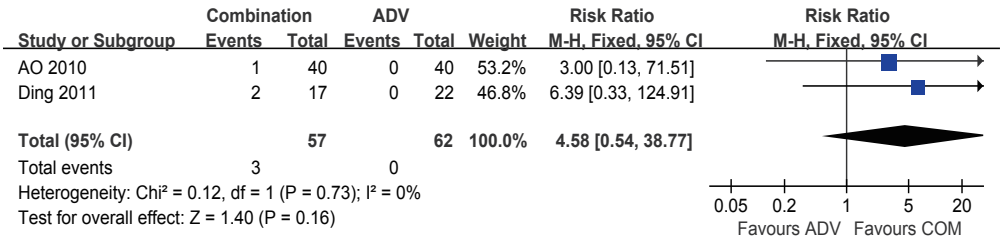

Figure 9 HBsAg clearance rates, subgroup analysis of PEG-IFN α+ADV vs ADV in the treatment of Chinese hepatitis B patients.

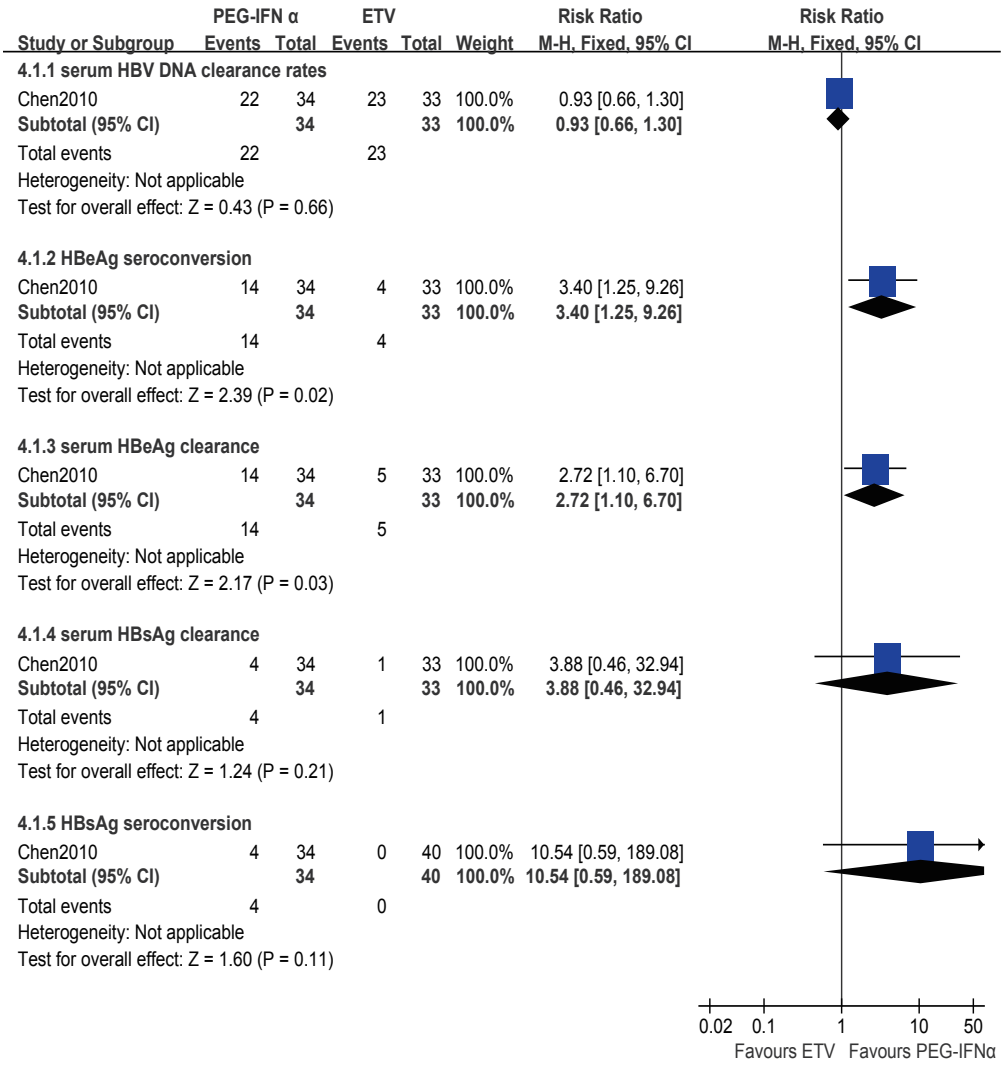

Figure 10 Subgroup analysis of serum HBV DNA clearance, HBeAg and HBsAg seroconversion, HBeAg and HBsAg clearance rates between PEG-IFN α and ETV monotherapy.

3 Discussion

The important goal of chronic hepatitis B treatment is completely clear or sustained suppression of HBV, so as to reduce the inflammation of the liver and prevention of liver fibrosis, hepatic decompensation, hepatocellular carcinoma, and prolong the survival period of patients ultimately. Therefore, antiviral treatment is the key to CHB therapy. PEG-IFN α is one of the common antiviral drugs used currently in western counties and then introduced to China. There are several publications and clinical trials come from western countries reported the advanced effects and safety of PEG-IFN α based therapy in the treatment of hepatitis B [7-10]. However, the situation in mainland China is that most CHB patients are come from rural areas, the high costs of PEG-IFN α treatment is unaffordable for most of them, which makes PEG-IFN efficacy assessment more difficult in China. Several new clinical trials to compare the efficiency of PEG-IFN α treatment with other antiviral regimes in patients with hepatitis B in China were published in recent years, but the numbers of patients included in these clinical trials are too small to draw a clear conclusion. Therefore, a new meta-analysis of comparing PEG-IFN α with other antiviral treatment regimens is needed to examine the beneficial effects of PEG-IFN α therapy in Chinese patients with hepatitis B.

Our meta-analysis show that in comparison with IFN α, PEG-IFN α attained higher ALT normalization rates, serum HBV DNA clearance rates, HBeAg seroconversion rates and serum HBeAg clearance rates at all treatment point and follow-up point in hepatitis B patients than IFN α treatment except for the 24th week of treatment of ALT normalization rate in China. Besides, PEG-IFN α therapy was more effective than IFN α therapy in the improvement of serum liver fibrosis related biomarkers, including HA, PC-III, IV-c and LN. All this found in this study

supported that PEG-IFN α is more effective than IFN α in the treatment of CHB patients in China. Evidence-based studies have demonstrated the efficacy of PEG-IFN α-2a treatment versus IFN α in China in 2010[27], our meta-analysis is an undated and extended report on the clinical effectiveness of PEG-IFN α for the treatment of CHB by adding several new published RCTs recently including PEG-IFN α-2b therapy and assess the quality by Jadad score.

In the comparison of PEG-IFN α group versus ETV group for CHB in China, PEG-IFN α showed superiority in the serological response than ETV, statistically higher rate were found in HBeAg seroconversion rate and HBeAg clearance rates by PEG-IFN α. Although PEG-IFN α is effective than ETV in the virological response, the improvement of HBeAg seroconversion rate and HBeAg clearance rates is not satisfaction. In future trials, the course of PEG-IFN α treatment should be extended to conducive to better efficacy in China.

The situation between the PEG-IFN α and ADV combination group versus ADV monotherapy show statistically higher rate in HBeAg seroconversion rates in the combination group in all treatment point and follow-up point. Higher rate of ALT normalization was obtained in 48th week of follow-up, higher rate of serum HBV DNA clearance was obtained in 48th treatment. Up to data, several trials involving PEG-IFN α and ADV combination therapy had been reported in western countries[28-30], marked decreases in serum HBV DNA and favorable HBeAg seroconversion and clearance rates were achieved in the combination group than ADV monotherapy. Research has revealed that PEG-IFN α have effects of immunoregulation and antiviral protein inductions thus lead to higher serological response and sustained virological response, but the inhibitor effect to virus is weak; ADV has strong antiviral activity and onset rapidly, the resistance is rarely to happen, but the HBeAg seroconversion is always low. Therefore, combination therapy of PEG-IFN α and ADV has a strong complementary, which had been confirmed in this study. However, data are too limited to exclude a substantial benefit or harm of PEG-IFN α combination therapy and also to support recommending for the treatment of chronic hepatitis B in China.

Evidence-based studies have demonstrated that efficacy of IFN α treatment relates to HBV genotypes[31]. A Meta analysis[32] and a pooled analysis of over 1200 patients [33] provide compelling support for the idea that genotype A is the most treatment-responsive genotype in HBeAg-positive hepatitis B. However, no epidemiological study with a sufficient number of cases has shown an effect of HBV genotypes on the rate of HBV chronicity in China. In the future study, analysis on the effects of PEG-IFN α based on HBV genotype in CHB patients is needed in China.

The objective and accuracy results of meta-analysis depend on the comprehensive and high-quality literature. In this study, the total quality of literatures is poor. All the included trials did not specifically describe the randomization scheme and the use of blind method, only 4 of our 16 studies reported subjects withdraw or drop out. Besides, the majority of the included trials are in small sample size. In future trials, we hope that Chinese investigators take relatively simple measures such as random number generating software in trials to compare different therapies. High quality trials of large, randomized, multicentre design are also needed to make credible decision.

In conclusion, PEG-IFN α therapy was more effective than IFN α therapy in achieving ALT normalization, serum HBV DNA clearance, HBeAg seroconversion, serum HBeAg clearance and hepatic fibrosis improvement in CHB patients in China. PEG-IFN α was obviously superior to ETV in HBeAg seroconversion and serum HBeAg clearance. The combination therapy of PEG-IFN α and ADV was effective than ADV monotherapy in ALT normalization, serum HBV DNA clearance and HBeAg seroconversion. PEG-IFN α showed no priority to other treatment regimes in HBsAg clearance. Treatment with PEG-IFN α appears to be effective and safe, and can be prescribed as first-line treatment options for CHB patients in China. Data are too limited to exclude a substantial benefit or harm of PEG-IFN α combination therapy for CHB patients in China.

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本刊常用词汇英文缩写表

从2012年第1期开始，本刊对大家较熟悉的以下常用词汇，允许直接使用缩写，即首次出现时可不标注中文。

C- 反应蛋白	CRP	甲型肝炎病毒	HAV	纤连蛋白	FN
Toll 样受体	TLRs	碱性成纤维细胞转化生长因子	bFGF	心电图	ECG
氨基末端激酶	JNK	聚合酶链反应	PCR	心脏监护病房	CCU
白细胞	WBC	抗生物素蛋白 - 生物素酶复合物法	ABC 法	血管紧张素 II	Ang II
白细胞介素	IL	辣根过氧化物酶	HRP	血管内皮生长因子	VEGF
半数抑制浓度	IC_{50}	链霉抗生物素蛋白 - 生物素酶复合物法	SABC 法	血管性血友病因子	vWF
变异系数	CV	磷酸盐缓冲液	PBS	血红蛋白	Hb
标记的链霉抗生物素蛋白 - 生物素法	SP 法	绿色荧光蛋白	GFP	血肌酐	SCr
表皮生长因子	EGF	酶联免疫吸附测定	ELISA	血尿素氮	BUN
丙氨酸转氨酶	ALT	美国食品药品管理局	FDA	血小板	PLT
丙二醛	MDA	脑电图	EEG	血压	BP
丙型肝炎病毒	HCV	内毒素 / 脂多糖	LPS	血氧饱和度	SO_2
超氧化物歧化酶	SOD	内皮型一氧化氮合酶	eNOS	烟酰胺腺嘌呤二核苷酸	NADPH
磁共振成像	MRI	内生肌酐清除率	CCr	严重急性呼吸综合征	SARS
极低密度脂蛋白胆固醇	VLDL-C	尿素氮	BUN	一氧化氮	NO
低密度脂蛋白胆固醇	LDL-C	凝血酶时间	TT	一氧化氮合酶	NOS
动脉血二氧化碳分压	$PaCO_2$	凝血酶原时间	PT	乙二胺四乙酸	EDTA
动脉血氧分压	PaO_2	牛血清白蛋白	BSA	乙酰胆碱	ACh
二甲基亚砜	DMSO	热休克蛋白	HSP	乙型肝炎病毒	HBV
反转录 - 聚合酶链反应	RT-PCR	人类免疫缺陷病毒	HIV	乙型肝炎病毒 e 抗体	HBeAb
辅助性 T 细胞	Th	人绒毛膜促性腺激素	HCG	乙型肝炎病毒 e 抗原	HBeAg
肝细胞生长因子	HGF	三磷酸腺苷	ATP	乙型肝炎病毒表面抗体	HBsAb
干扰素	IFN	三酰甘油	TG	乙型肝炎病毒表面抗原	HBsAg
高密度脂蛋白胆固醇	HDL-C	生理氯化钠溶液	NS	乙型肝炎病毒核心抗体	HBcAb
谷胱甘肽	GSH	世界卫生组织	WHO	乙型肝炎病毒核心抗原	HBcAg
固相 pH 梯度	IPG	双蒸水	ddH_2O	异硫氰酸荧光素	FLTC
核糖核酸	RNA	丝裂原活化蛋白激酶	MAPK	诱导型一氧化氮合酶	iNOS
核因子 -κB	NF-κB	四甲基偶氮唑盐微量酶反应	MTT	原位末端标记法	TUNEL
红细胞	RBC	苏木精 - 伊红染色	HE	杂合性缺失	LOH
红细胞沉降率	ESR	胎牛血清	FBS	增强化学发光法	ECL
环氧化酶 -2	COX-2	体质量指数	BMI	肿瘤坏死因子	TNF
活化部分凝血活酶时间	APTT	天冬氨酸氨基转移酶	AST	重症监护病房	ICU
活性氧	ROS	脱氧核糖核酸	DNA	转化生长因子	TGF
获得性免疫缺陷综合征	AIDS	细胞间黏附分子	ICAM	自然杀伤细胞	NK 细胞
肌酐	Cr	细胞外基质	ECM	总胆固醇	TC
基质金属蛋白酶	MMP	细胞外调节蛋白激酶	ERK	总胆红素	Tbil
计算机 X 线断层照相技术	CT				