・论 著・

1193

## · ARTICLES ·

DOI:10.3969/j.issn.1672-7347.2013.12.001 http://xbyx.xysm.net/xbwk/fileup/PDF/2013121193.pdf

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

DENG Zhenzhen, WANG Chunjiang, LI Zuojun, LI Bing, LIU Shikun

(Department of Pharmacy, Third Xiangya Hospital, Central South University, Changsha 410013, China)

#### ABSTRACT

**Objective:** To conduct a meta-analysis to determine the efficacy of peginterferon alpha (PEG-IFN  $\alpha$ ) therapy versus IFN  $\alpha$ , 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  $\alpha$  therapy for the treatment of chronic hepatitis B in China.

**Results:** Fourteen trials met the eligibility criteria for this Meta analysis. PEG-IFN  $\alpha$  therapy was more effective than IFN  $\alpha$  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  $\alpha$  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  $\alpha$  and ADV was more effective than ADV monotherapy in ALT normalization, serum HBV DNA clearance and HBeAg seroconversion (*P*<0.05). PEG-IFN  $\alpha$  showed no priority to other treatment regimes in HBsAg clearance.

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

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

Date of reception: 2013-03-05

**Biography:** DENG Zhenzhen, master, pharmacist, mainly engaged in the research of chronic hepatic disease. **Corresponding author:** LIU Shikun, Email: l8618496@126.com

# 聚乙二醇干扰素a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

邓珍珍,王春江,李佐军,李兵,刘世坤 (中南大学湘雅三医院药剂科,长沙410013)

[关键词] PEG-IFN a; Meta分析; HBeAg阳性; 慢性乙型肝炎

Hepatitis B virus (HBV) infection is a serious global public health problem<sup>[1]</sup>. 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<sup>[2]</sup>. 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<sup>[3]</sup>. 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<sup>[4-5]</sup>. 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  $\alpha$  (IFN  $\alpha$ ) and peg interferon alpha (PEG-IFN  $\alpha$ ) based treatment, and sustained, off-therapy response is more often followed by relapse<sup>[6]</sup>.

Conventional IFN  $\alpha$  is approved first-line treatments of chronic HBV infection for a number of years. IFN  $\alpha$ 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  $\alpha$  include contraindication in patients with decompensated liver disease, and clinically significant side effects. Treatment of CHB with PEG-IFN  $\alpha$  has been reported in several independent studies. These studies suggest a more promising result treating PEG-IFN  $\alpha$  than conventional interferon or lamivudine<sup>[7-10]</sup>, and PEG-IFN  $\alpha$ was recommended as first-line treatment regime for CHB.

However, the actual situation in mainland China is that the clinical acceptance of PEG-IFN  $\alpha$  treatment is generally low for CHB patients for its high costs, which makes PEG-IFN  $\alpha$  efficacy assessment more difficult in China<sup>[11]</sup>, so the optimal choice for individual patients remains controversial. In recent years, several new clinical trials to compare the efficiency of PEG-IFN  $\alpha$  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  $\alpha$  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  $\alpha$  based therapy for HBeAg-positive CHB infection and provide the basis for evidence-based decision making in clinical settings.

# I MATERIALS AND METHODS

#### **I.I 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  $\alpha$ , treatment and trial. In addition, a manual search based on reference lists from previous publications involving PEG-IFN  $\alpha$  treatment was conducted.

#### **I.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.

#### **I.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<sup>[12]</sup>.

#### 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  $(\chi^2)$  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 fixedeffect method was used to combine the results. When heterogeneity was confirmed ( $P \leq 0.1$ ), the random-effect method was used. The overall effect was tested using Zscores, 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  $\alpha$  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  $\alpha$  and IFN  $\alpha$ 

therapies<sup>[13-22]</sup>, three are comparison of combination of PEG-IFN  $\alpha$  and ADV with ADV monotherapy<sup>[23-25]</sup> and one is comparison of PEG-IFN  $\alpha$  and ETV therapies<sup>[26]</sup>. 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.

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

Table 1 Characteristics of the trials included in the Meta analysis

# **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  $\alpha$  than for patients treated with IFN  $\alpha$  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  $\alpha$  [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.

1.1.1 24 weeks treatment         Cheng 2007       10         Li 2010       26         Nie 2008       28         Sun 2009       8         Zhao 2006       59         Zhong 2010       19         Subtotal (95% CI)       100         Total events       150         Heterogeneity: Tau² = 0.00; Chi       10         Test for overall effect: Z = 4.37       1.1.2 48 weeks treatment         Cheng 2007       20         Li 2010       32         Nie 2008       300         Sun 2009       13         Zhong 2010       20         Subtotal (95% CI)       100         Total events       139         Heterogeneity: Tau² = 0.01; Chi       139         Heterogeneity: Tau² = 0.01; Chi       150         Total events       139         Heterogeneity: Tau² = 0.01; Chi       30         Sun 2009       14         Zhao 2006       41         Subtotal (95% CI)       100         Total events       85         Heterogeneity: Tau² = 0.10; Chi       10; Chi         Total events       85         Heterogeneity: Tau² = 0.10; Chi       10; Chi	27 39 33 25 115 22 <b>261</b> 2 <sup>2</sup> = 3.32 (P < 0.0) 27 40 39 33 25 22 <b>186</b> 2 <sup>2</sup> = 5.81 (P < 0.0) 39 25	11 14 21 39 14 101 , df = 5 (P 001) 15 14 17 23 4 15 88 , df = 5 (P	34 38 33 21 115 22 <b>263</b> 9 = 0.65 34 40 38 33 21 22 <b>188</b>	1.8% 3.8% 9.2% 0.4% 8.3% 6.5% <b>30.0%</b> ); I <sup>2</sup> = 0% 4.4% 3.5% 5.7% 12.4% 1.0% 8.2% <b>35.0%</b> ); I <sup>2</sup> = 14%	M-H, Random, 95% Cl 1.14 [0.57, 2.29] 1.81 [1.13, 2.90] 1.33 [0.99, 1.79] 3.36 [0.80, 14.14] 1.51 [1.11, 2.06] 1.36 [0.95, 1.94] 1.44 [1.22, 1.70] 1.44 [1.22, 1.70] 1.68 [1.08, 2.60] 1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79] 1.83 [1.21, 2.75]	M-H, Random, 95% Cl
Cheng 2007       10         Li 2010       26         Nie 2008       28         Sun 2009       8         Zhao 2006       59         Zhong 2010       19         Subtotal (95% CI)       100         Total events       150         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi       11         Test for overall effect: Z = 4.37       11.2 48 weeks treatment         Cheng 2007       20         Li 2010       32         Nie 2008       30         Sun 2009       13         Zhong 2010       20         Subtotal (95% CI)       100         Total events       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       139         Li 2010       30         Sun 2009       14         Zhao 2006       41         Subtotal (95% CI)       30         Total events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       30         Subtotal (95% CI)       30         Total events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       30         Subtotal (95% CI)       30         T	39 33 25 115 22 <b>261</b> 2° = 3.32 (P < 0.0 27 40 39 33 25 22 <b>186</b> 2° = 5.81 (P < 0.0 39 25 115	14 21 39 14 101 , df = 5 (P 001) 15 14 17 23 4 15 88 , df = 5 (P 0001) 16	38 33 21 115 22 <b>263</b> 9 = 0.65 34 40 38 33 21 22 <b>188</b> 9 = 0.33 38	$\begin{array}{c} 3.8\% \\ 9.2\% \\ 0.4\% \\ 8.3\% \\ 6.5\% \\ \textbf{30.0\%} \end{array}$ ); $ ^2 = 0\% \\ \begin{array}{c} 4.4\% \\ 3.5\% \\ 5.7\% \\ 12.4\% \\ 1.0\% \\ 8.2\% \\ \textbf{35.0\%} \end{array}$ ); $ ^2 = 14\% \\ 5.0\% \end{array}$	1.81 [1.13, 2.90] 1.33 [0.99, 1.79] 3.36 [0.80, 14.14] 1.51 [1.11, 2.06] 1.36 [0.95, 1.94] 1.44 [1.22, 1.70] 1.68 [1.08, 2.60] 1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	
.i 2010       26         Nie 2008       28         Sun 2009       8         Zhao 2006       59         Zhong 2010       19         Subtotal (95% CI)       100         Total events       150         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi       11.12         Test for overall effect: Z = 4.37       1.1.2         I.1.2 48 weeks treatment       11.12         Cheng 2007       20         Li 2009       24         Li 2010       32         Sun 2009       13         Zhong 2010       20         Subtotal (95% CI)       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       14         Test for overall effect: Z = 4.78       1.1.3 24 weeks follow-up         Li 2010       30         Sun 2009       14         Zhao 2006       41         Subtotal (95% CI)       100         Total events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       100         Subtotal (95% CI)       100         Total events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       100         Subtotal (95% CI)	39 33 25 115 22 <b>261</b> 2° = 3.32 (P < 0.0 27 40 39 33 25 22 <b>186</b> 2° = 5.81 (P < 0.0 39 25 115	14 21 39 14 101 , df = 5 (P 001) 15 14 17 23 4 15 88 , df = 5 (P 0001) 16	38 33 21 115 22 <b>263</b> 9 = 0.65 34 40 38 33 21 22 <b>188</b> 9 = 0.33 38	$\begin{array}{c} 3.8\% \\ 9.2\% \\ 0.4\% \\ 8.3\% \\ 6.5\% \\ \textbf{30.0\%} \end{array}$ ); $ ^2 = 0\% \\ \begin{array}{c} 4.4\% \\ 3.5\% \\ 5.7\% \\ 12.4\% \\ 1.0\% \\ 8.2\% \\ \textbf{35.0\%} \end{array}$ ); $ ^2 = 14\% \\ 5.0\% \end{array}$	1.81 [1.13, 2.90] 1.33 [0.99, 1.79] 3.36 [0.80, 14.14] 1.51 [1.11, 2.06] 1.36 [0.95, 1.94] 1.44 [1.22, 1.70] 1.68 [1.08, 2.60] 1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	
Nie 2008       28         Sun 2009       8         Zhao 2006       59         Zhong 2010       19         Subtotal (95% CI)       150         Total events       150         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi       150         Test for overall effect: Z = 4.37       1.1.2 48 weeks treatment         Cheng 2007       20         Li 2009       24         Li 2010       32         Sun 2009       13         Zhong 2010       20         Subtotal (95% CI)       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       30         Subtotal (95% CI)       30         Fotal events       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       30         Sun 2009       14         Zhao 2006       41         Subtotal (95% CI)       50         Fotal events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         Fotal events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         Fotal events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi	33 25 115 22 261 2 = 3.32 27 40 39 33 25 22 186 2 = 5.81 (P < 0.0) 39 25 115	21 2 39 14 101 , df = 5 (P 001) 15 14 17 23 4 15 88 , df = 5 (P 0001) 16	33 21 115 22 <b>263</b> 9 = 0.65 34 40 38 33 21 22 <b>188</b> 9 = 0.33 38	9.2% 0.4% 8.3% 6.5% <b>30.0%</b> ); I <sup>2</sup> = 0% 4.4% 3.5% 5.7% 12.4% 1.0% 8.2% <b>35.0%</b> ); I <sup>2</sup> = 14% 5.0%	1.33 [0.99, 1.79] 3.36 [0.80, 14.14] 1.51 [1.11, 2.06] 1.36 [0.95, 1.94] 1.44 [1.22, 1.70] 1.44 [1.22, 1.70] 1.68 [1.08, 2.60] 1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	
Sun 2009         8           Sun 2006         59           Zhao 2006         59           Zhong 2010         19           Subtotal (95% CI)         50           Fotal events         150           Heterogeneity: Tau <sup>2</sup> = 0.00; Chi         59           Test for overall effect: Z = 4.37         1.1.2 48 weeks treatment           Cheng 2007         20           Li 2009         24           Li 2010         32           Nie 2008         30           Sun 2009         13           Zhong 2010         20           Subtotal (95% CI)         50           Total events         139           Heterogeneity: Tau <sup>2</sup> = 0.01; Chi         50           Fest for overall effect: Z = 4.78         1.1.3 24 weeks follow-up           Li 2010         30           Sun 2009         14           Zhao 2006         41           Subtotal (95% CI)         50           Fotal events         85           Heterogeneity: Tau <sup>2</sup> = 0.10; Chi           Fotal events         85           Heterogeneity: Tau <sup>2</sup> = 0.10; Chi           Fotal events         85           Heterogeneity: Tau <sup>2</sup> = 0.10; Chi	25 115 22 261 2 = 3.32 27 40 39 33 25 22 186 2 = 5.81 (P < 0.0) 39 25 115	2 39 14 101 , df = 5 (P 001) 15 14 17 23 4 15 88 , df = 5 (P 0001) 16	21 115 22 263 9 = 0.65 34 40 38 33 21 22 188 9 = 0.33	0.4% 8.3% 6.5% <b>30.0%</b> );   <sup>2</sup> = 0% 4.4% 3.5% 5.7% 12.4% 1.0% 8.2% <b>35.0%</b> );   <sup>2</sup> = 14% 5.0%	3.36 [0.80, 14.14] 1.51 [1.11, 2.06] 1.36 [0.95, 1.94] 1.44 [1.22, 1.70] 1.68 [1.08, 2.60] 1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	
Zhao 2006       59         Zhong 2010       19         Subtotal (95% CI)       Fotal events       150         Fotal events       150         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi       Fotal events       150         Fest for overall effect: Z = 4.37       I.1.2 48 weeks treatment       I.1.2 48 weeks treatment         Cheng 2007       20	115 22 261 2 = 3.32 (P < 0.0 27 40 39 33 25 22 186 2 = 5.81 (P < 0.0 39 25 115	39 14 101 , df = 5 (P 001) 15 14 17 23 4 15 88 , df = 5 (P 0001) 16	115 22 263 9 = 0.65 34 40 38 33 21 22 188 9 = 0.33 38	8.3% 6.5% <b>30.0%</b> ); I <sup>2</sup> = 0% 4.4% 3.5% 5.7% 12.4% 1.0% 8.2% <b>35.0%</b> ); I <sup>2</sup> = 14% 5.0%	1.51 [1.11, 2.06] 1.36 [0.95, 1.94] 1.44 [1.22, 1.70] 1.68 [1.08, 2.60] 1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	
Zhong 2010       19         Subtotal (95% CI)       150         Fotal events       150         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi       Fost for overall effect: $Z = 4.37$ I.1.2 48 weeks treatment       20         Cheng 2007       20         .i 2009       24         .i 2010       32         Nie 2008       30         Sun 2009       13         Zhong 2010       20         Subtotal (95% CI)       50         Fotal events       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       70         Fest for overall effect: Z = 4.78       1.1.3 24 weeks follow-up         .i 2010       30         Sun 2009       14         Zhao 2006       41         Subtotal (95% CI)       50         Fotal events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         Fotal events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         Fotal events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         Fest for overall effect: Z = 1.65         I.1.4 48 weeks follow-up	22 261 <sup>2</sup> = 3.32 (P < 0.0 27 40 39 33 25 22 186 <sup>2</sup> = 5.81 (P < 0.0 39 25 115	14 101 df = 5 (F 001) 15 14 17 23 4 15 88 df = 5 (F 0001) 16	22 263 9 = 0.65 34 40 38 33 21 22 188 9 = 0.33 38	6.5% 30.0% );   <sup>2</sup> = 0% 4.4% 3.5% 5.7% 12.4% 1.0% 8.2% 35.0% );   <sup>2</sup> = 14% 5.0%	1.36 [0.95, 1.94] 1.44 [1.22, 1.70] 1.68 [1.08, 2.60] 1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	
Subtotal (95% CI)           Fotal events         150           Teterogeneity: Tau <sup>2</sup> = 0.00; Chi           Fest for overall effect: Z = 4.37           I.1.2 48 weeks treatment           Cheng 2007         20           .i 2009         24           .i 2010         32           Nie 2008         30           Subtotal (95% CI)         50           Fotal events         139           Heterogeneity: Tau <sup>2</sup> = 0.01; Chi         50           Fest for overall effect: Z = 4.78         1.1.3 24 weeks follow-up           .i 2010         30           Sun 2009         14           Zhao 2006         41           Subtotal (95% CI)         50           Fotal events         85           Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         50           Subtotal (95% CI)         50           Fotal events         85           Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         50           Fotal events         85           Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         50           Fest for overall effect: Z = 1.65         1.1.4 48 weeks follow-up	261 <sup>2</sup> = 3.32 (P < 0.0) 27 40 39 33 25 22 186 <sup>2</sup> = 5.81 (P < 0.0) 39 25 115	101 , df = 5 (P 001) 15 14 17 23 4 15 88 , df = 5 (P 0001) 16	263 9 = 0.65 34 40 38 33 21 22 188 9 = 0.33 38	30.0% );   <sup>2</sup> = 0% 4.4% 3.5% 5.7% 12.4% 1.0% 8.2% 35.0% );   <sup>2</sup> = 14% 5.0%	1.44 [1.22, 1.70] 1.68 [1.08, 2.60] 1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	
Total events       150         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi         Fest for overall effect: Z = 4.37         1.1.2 48 weeks treatment         Cheng 2007       20         Li 2009       24         Li 2010       32         Nie 2008       30         Sun 2009       13         Zhong 2010       20         Subtotal (95% CI)       5         Fotal events       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       7         Fest for overall effect: Z = 4.78       1.1.3 24 weeks follow-up         Li 2010       30         Sun 2009       14         Zhao 2006       41         Subtotal (95% CI)       7         Fotal events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       7         Fotal events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       7         Fotal events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       7         Fotal events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       7         Fotal events       85         Heterogeneity: Tau <sup>2</sup> = 1.65         1.1.4 48 weeks follow-up	2 = 3.32 (P < 0.0) 27 40 39 33 25 22 <b>186</b> 2 = 5.81 (P < 0.0) 39 25 115	, df = 5 (F 001) 15 14 17 23 4 15 88 , df = 5 (F 0001) 16	9 = 0.65 34 40 38 33 21 22 <b>188</b> 9 = 0.33 38	);   <sup>2</sup> = 0% 4.4% 3.5% 5.7% 12.4% 1.0% 8.2% <b>35.0%</b> );   <sup>2</sup> = 14% 5.0%	1.68 [1.08, 2.60] 1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] <b>1.51 [1.28, 1.79]</b>	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi         Test for overall effect: Z = 4.37 <b>1.1.2 48 weeks treatment</b> Cheng 2007       20         Li 2009       24         Li 2010       32         Nie 2008       30         Sun 2009       13         Zhong 2010       20         Subtotal (95% CI)       Total events         Total events       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       Test for overall effect: Z = 4.78 <b>1.1.3 24 weeks follow-up</b>	<sup>2</sup> = 3.32 (P < 0.0) 27 40 39 33 25 22 <b>186</b> <sup>2</sup> = 5.81 (P < 0.0) 39 25 115	, df = 5 (F 001) 15 14 17 23 4 15 88 , df = 5 (F 0001) 16	34 40 38 33 21 22 <b>188</b> 9 = 0.33	4.4% 3.5% 5.7% 12.4% 1.0% 8.2% <b>35.0%</b> ); I <sup>2</sup> = 14% 5.0%	1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	
Test for overall effect: $Z = 4.37$ <b>1.1.2 48 weeks treatment</b> Cheng 2007       20         Li 2009       24         Li 2010       32         Nie 2008       30         Sun 2009       13         Zhong 2010       20         Subtotal (95% CI)       70         Total events       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       70         Test for overall effect: $Z = 4.78$ 1.1.3 24 weeks follow-up         Li 2010       30         Sun 2009       14         Zhao 2006       41         Subtotal (95% CI)       70         Total events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       70         Total events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       70         Total events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       70         Test for overall effect: Z = 1.65       1.1.4 48 weeks follow-up	(P < 0.0) 27 40 39 33 25 22 <b>186</b> 2 = 5.81 (P < 0.0) 39 25 115	001) 15 14 17 23 4 15 88 , df = 5 (P 0001) 16	34 40 38 33 21 22 <b>188</b> 9 = 0.33	4.4% 3.5% 5.7% 12.4% 1.0% 8.2% <b>35.0%</b> ); I <sup>2</sup> = 14% 5.0%	1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	
Cheng 2007       20         Li 2009       24         Li 2010       32         Nie 2008       30         Sun 2009       13         Zhong 2010       20         Subtotal (95% CI)       7         Total events       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       7         Test for overall effect: Z = 4.78       1.1.3 24 weeks follow-up         Li 2010       30         Sun 2009       14         Zhao 2006       41         Subtotal (95% CI)       7         Total events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       7         Total events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       7         Test for overall effect: Z = 1.65       1.1.4 48 weeks follow-up	40 39 33 25 22 <b>186</b> (P < 0.0) 39 25 115	14 17 23 4 15 88 , df = 5 (P 0001) 16	40 38 33 21 22 <b>188</b> 9 = 0.33	3.5% 5.7% 12.4% 1.0% 8.2% <b>35.0%</b> ); I <sup>2</sup> = 14% 5.0%	1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	
i 2009       24         i 2010       32         xie 2008       30         Sun 2009       13         Zhong 2010       20         Subtotal (95% CI)       7         Fotal events       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       7         Fest for overall effect: Z = 4.78       1.1.3 24 weeks follow-up         Li 2010       30         Sun 2009       14         Zhao 2006       41         Subtotal (95% CI)       7         Fotal events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       7         Subtotal (95% CI)       85         Fotal events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       7         Fest for overall effect: Z = 1.65       1.1.4 48 weeks follow-up	40 39 33 25 22 <b>186</b> (P < 0.0) 39 25 115	14 17 23 4 15 88 , df = 5 (P 0001) 16	40 38 33 21 22 <b>188</b> 9 = 0.33	3.5% 5.7% 12.4% 1.0% 8.2% <b>35.0%</b> ); I <sup>2</sup> = 14% 5.0%	1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	
Li 2009       24         Li 2010       32         Nie 2008       30         Sun 2009       13         Zhong 2010       20         Subtotal (95% CI)       139         Total events       139         Heterogeneity: Tau² = 0.01; Chi       150         Test for overall effect: Z = 4.78       1.1.3 24 weeks follow-up         Li 2010       30         Sun 2009       14         Zhao 2006       41         Subtotal (95% CI)       10         Total events       85         Heterogeneity: Tau² = 0.10; Chi       10; Chi         Test for overall effect: Z = 1.65       1.1.4 48 weeks follow-up	40 39 33 25 22 <b>186</b> (P < 0.0) 39 25 115	14 17 23 4 15 88 , df = 5 (P 0001) 16	40 38 33 21 22 <b>188</b> 9 = 0.33	3.5% 5.7% 12.4% 1.0% 8.2% <b>35.0%</b> ); I <sup>2</sup> = 14% 5.0%	1.71 [1.05, 2.80] 1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	
Li 2010 32 Nie 2008 30 Sun 2009 13 Zhong 2010 20 <b>Subtotal (95% CI)</b> Total events 139 Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: Z = 4.78 <b>1.1.3 24 weeks follow-up</b> Li 2010 30 Sun 2009 14 Zhao 2006 41 <b>Subtotal (95% CI)</b> Total events 85 Heterogeneity: Tau <sup>2</sup> = 0.10; Chi Test for overall effect: Z = 1.65 <b>1.1.4 48 weeks follow-up</b>	39 33 25 22 <b>186</b> (P < 0.0) 39 25 115	17 23 4 15 88 , df = 5 (P 0001) 16	38 33 21 22 <b>188</b> 9 = 0.33	5.7% 12.4% 1.0% 8.2% <b>35.0%</b> ); I <sup>2</sup> = 14% 5.0%	1.83 [1.25, 2.69] 1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	• • •
Nie 2008         30           Sun 2009         13           Zhong 2010         20           Subtotal (95% CI)         139           Total events         139           Heterogeneity: Tau <sup>2</sup> = 0.01; Chi         139           Test for overall effect: Z = 4.78         1.1.3 24 weeks follow-up           Li 2010         30           Sun 2009         14           Zhao 2006         41           Subtotal (95% CI)         104           Total events         85           Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         105           Total events         85           Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         105           Test for overall effect: Z = 1.65         1.1.4 48 weeks follow-up	33 25 22 <b>186</b> 2° = 5.81 (P < 0.0) 39 25 115	23 4 15 88 , df = 5 (P 0001) 16	33 21 22 <b>188</b> 9 = 0.33	12.4% 1.0% 8.2% <b>35.0</b> % ); I <sup>2</sup> = 14% 5.0%	1.30 [1.02, 1.67] 2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	•
Sun 2009         13           Zhong 2010         20           Subtotal (95% CI)         139           Total events         139           Heterogeneity: Tau <sup>2</sup> = 0.01; Chi         117           Test for overall effect: Z = 4.78         1.1.3 24 weeks follow-up           Li 2010         30           Sun 2009         14           Zhao 2006         41           Subtotal (95% CI)         100           Total events         85           Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         105           Total events         85           Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         105           Test for overall effect: Z = 1.65         1.1.4 48 weeks follow-up	25 22 186 2 = 5.81 (P < 0.0) 39 25 115	4 15 88 , df = 5 (P 0001) 16	21 22 <b>188</b> 9 = 0.33 38	1.0% 8.2% <b>35.0%</b> ); I <sup>2</sup> = 14% 5.0%	2.73 [1.05, 7.12] 1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	•
Zhong 2010       20         Subtotal (95% CI)       139         Total events       139         Heterogeneity: Tau <sup>2</sup> = 0.01; Chi       117         Test for overall effect: Z = 4.78       1.1.3 24 weeks follow-up         Li 2010       30         Sun 2009       14         Zhao 2006       41         Subtotal (95% CI)       10         Total events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       10; Chi         Test for overall effect: Z = 1.65       1.1.4 48 weeks follow-up	22 <b>186</b> <sup>2</sup> = 5.81 (P < 0.0) 39 25 115	15 88 , df = 5 (P 0001) 16	22 188 9 = 0.33 38	8.2% <b>35.0%</b> );   <sup>2</sup> = 14% 5.0%	1.33 [0.97, 1.83] 1.51 [1.28, 1.79]	<b>•</b>
Subotal (95% CI)           Total events         139           Heterogeneity: Tau <sup>2</sup> = 0.01; Chi           Test for overall effect: Z = 4.78           1.1.3 24 weeks follow-up           Li 2010         30           Sun 2009         14           Zhao 2006         41           Subtotal (95% CI)         85           Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         Total events           Test for overall effect: Z = 1.65         1.1.4 48 weeks follow-up	<b>186</b> <sup>2</sup> = 5.81 (P < 0.0) 39 25 115	88 , df = 5 (P 0001) 16	<b>188</b> 9 = 0.33 38	<b>35.0%</b> ); I <sup>2</sup> = 14% 5.0%	1.51 [1.28, 1.79]	<ul> <li>▲</li> <li>—</li> </ul>
Total events139Heterogeneity: Tau² = 0.01; ChiTest for overall effect: Z = 4.781.1.3 24 weeks follow-upLi 2010Sun 200914Zhao 2006Subtotal (95% CI)Total eventsHeterogeneity: Tau² = 0.10; ChiTest for overall effect: Z = 1.651.1.4 48 weeks follow-up	² = 5.81 (P < 0.0) 39 25 115	, df = 5 (P 0001) 16	9 = 0.33 38	); I² = 14% 5.0%		
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi         Test for overall effect: Z = 4.78         1.1.3 24 weeks follow-up         Li 2010       30         Sun 2009       14         Zhao 2006       41         Subtotal (95% CI)       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       Total events         Test for overall effect: Z = 1.65       1.1.4 48 weeks follow-up	<sup>2</sup> = 5.81 (P < 0.0) 39 25 115	, df = 5 (P 0001) 16	38	5.0%		
Test for overall effect: Z = 4.78         1.1.3 24 weeks follow-up         Li 2010       30         Sun 2009       14         Zhao 2006       41         Subtotal (95% CI)       70         Total events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         Test for overall effect: Z = 1.65         1.1.4 48 weeks follow-up	(P < 0.0 39 25 115	0001) 16	38	5.0%		
Sun 2009         14           Zhao 2006         41           Subtotal (95% CI)         41           Total events         85           Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         51           Test for overall effect: Z = 1.65         1.1.4 48 weeks follow-up	25 115				1 83 [1 21 2 75]	
Zhao 2006       41         Subtotal (95% CI)       10         Total events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi       10; Chi         Test for overall effect: Z = 1.65       1.1.4 48 weeks follow-up	115	6	04	4 = 0/	1.00 [1.21, 2.70]	
Subtotal (95% CI)         Total events       85         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi         Test for overall effect: Z = 1.65         1.1.4 48 weeks follow-up			21	1.5%	1.96 [0.92, 4.19]	
Total events85Heterogeneity: Tau² = 0.10; ChiTest for overall effect: Z = 1.651.1.4 48 weeks follow-up	179	40	115	6.7%	1.02 [0.72, 1.46]	
Heterogeneity: Tau <sup>2</sup> = 0.10; Chi Test for overall effect: Z = 1.65 1.1.4 48 weeks follow-up			174	13.2%	1.46 [0.93, 2.30]	
Test for overall effect: Z = 1.65		62				
			9 = 0.07	); I² = 63%		
Cheng 2007 18	27	12	34	3.1%	1.89 [1.11, 3.20]	
Cui 2006 22	40	17	40	4.1%	1.29 [0.82, 2.04]	+
Li 2009 26	40	16	40	4.3%	1.63 [1.04, 2.53]	
Nie 2008 29	33	21	33	9.6%	1.38 [1.04, 1.84]	
Sun 2009 16	25	3	21	0.7%	4.48 [1.51, 13.30]	
Subtotal (95% CI)	165		168	21.8%	1.58 [1.22, 2.05]	
Total events 111		69				
Heterogeneity: Tau <sup>2</sup> = 0.03; Chi Test for overall effect: Z = 3.49			9 = 0.20	); I² = 33%		
Total (95% CI)	791		793	100.0%	1.47 [1.34, 1.62]	•
Total events 485		320			- / -	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi			(P = 0.	39); l <sup>2</sup> = 5 <sup>0</sup>	% +	
Test for overall effect: Z = 8.08			, ,	,,	0.	2 0.5 1 2

Figure 1 ALT normalization rates, subgroup analysis of PEG-IFN a vs IFN a 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  $\alpha$  than for patients treated with IFN  $\alpha$  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  $\alpha$  [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.

Décembre a la Oct	PEG-IF		IFN			Risk Ratio	Risk Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.2.1 24 weeks treatm	ient						
Cheng 2007	10	27	11	34	3.2%	1.14 [0.57, 2.29]	
Gao 2008	13	30	7	31	2.2%	1.92 [0.89, 4.14]	
Li 2010	15	39	6	38	2.0%	2.44 [1.06, 5.61]	
Nie 2008	25	33	22	33	7.1%	1.14 [0.83, 1.55]	- <b>+</b>
Sun 2009	7	25	2	21	0.7%	2.94 [0.68, 12.67]	
Yi 2012	18	42	10	42	3.2%	1.80 [0.95, 3.43]	
Zhao 2006	43	115	34	115	11.0%	1.26 [0.88, 1.83]	+
Zhong 2010	17	22	13	22	4.2%	1.31 [0.86, 1.98]	+
Subtotal (95% CI)		333		336	33.6%	1.43 [1.18, 1.73]	•
Total events	148		105				
Heterogeneity: Chi <sup>2</sup> = 6	6.68. df = 7	7 (P = 0	.46):  ² =	0%			
Test for overall effect: 2		·					
	(	0.00	/•=/				
1.2.2 48 weeks treatm	ent						
Cheng 2007	15	27	10	34	2.9%	1.89 [1.02, 3.51]	
Gao 2008	16	30	9	31	2.9%	1.84 [0.96, 3.50]	<u>↓                                     </u>
Li 2009	21	40	12	40	3.9%	1.75 [1.00, 3.06]	<u> </u>
Li 2009	33	40 39	12	38	5.9%	1.79 [1.25, 2.56]	
Nie 2008	27	33	23	33	5.9 <i>%</i> 7.4%	1.17 [0.89, 1.55]	<b></b>
Sun 2009	10	25	23 4	21	1.4%	2.10 [0.77, 5.73]	
	21	25 42	4	42	3.6%	• • •	
Yi 2012			13	42	4.2%	1.91 [1.06, 3.45]	
Zhong 2010 Subtotal (95% CI)	18	22 258	15	261	4.2% 32.1%	1.38 [0.93, 2.06] 1.63 [1.37, 1.94]	
Subtotal (95% CI) Total events	161	200	100	201	32.1/0	1.03 [1.37, 1.94]	•
1.2.3 24 weeks follow	•		_		0.001		
Gao 2008	. 16	30	7	31	2.2%	2.36 [1.14, 4.91]	
Gao 2008 Li 2010	16 32	39	9	38	3.0%	3.46 [1.92, 6.25]	
Gao 2008 Li 2010 Sun 2009	16 32 12	39 25	9 4	38 21	3.0% 1.4%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66]	
Gao 2008 Li 2010 Sun 2009 Yi 2012	16 32 12 21	39 25 42	9 4 9	38 21 42	3.0% 1.4% 2.9%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006	16 32 12	39 25 42 115	9 4	38 21 42 115	3.0% 1.4% 2.9% 7.1%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI)	16 32 12 21 32	39 25 42	9 4 9 22	38 21 42	3.0% 1.4% 2.9%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events	16 32 12 21 32 113	39 25 42 115 <b>251</b>	9 4 9 22 51	38 21 42 115 <b>247</b>	3.0% 1.4% 2.9% 7.1%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5	16 32 12 21 32 113 5.31, df = 4	39 25 42 115 <b>251</b>	9 4 9 22 51 .26); I <sup>2</sup> =	38 21 42 115 <b>247</b>	3.0% 1.4% 2.9% 7.1%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events	16 32 12 21 32 113 5.31, df = 4	39 25 42 115 <b>251</b>	9 4 9 22 51 .26); I <sup>2</sup> =	38 21 42 115 <b>247</b>	3.0% 1.4% 2.9% 7.1%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34]	· · · · · · · · · · · · · · · · · · ·
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5 Test for overall effect: 2	16 32 12 21 32 113 5.31, df = 4 Z = 5.47 (F	39 25 42 115 <b>251</b> 4 (P = 0 P < 0.00	9 4 9 22 51 .26); I <sup>2</sup> =	38 21 42 115 <b>247</b> 25%	3.0% 1.4% 2.9% 7.1% <b>16.6%</b>	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34] 2.18 [1.65, 2.88]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5 Test for overall effect: 2 1.2.4 48 weeks follow- Cheng 2007	- 16 32 12 21 32 -113 5.31, df = 4 Z = 5.47 (F -up 14	39 25 42 115 <b>251</b> ↓ (P = 0 ○ < 0.00	9 4 9 22 51 .26); I <sup>2</sup> = 0001) 8	38 21 42 115 <b>247</b> 25% 34	3.0% 1.4% 2.9% 7.1% 16.6%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34] 2.18 [1.65, 2.88]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5 Test for overall effect: 2	16 32 12 21 32 113 5.31, df = 4 Z = 5.47 (F -up	39 25 42 115 <b>251</b> 4 (P = 0 P < 0.00	9 4 9 22 51 .26); I <sup>2</sup> = 0001)	38 21 42 115 <b>247</b> 25%	3.0% 1.4% 2.9% 7.1% 16.6% 2.3% 5.5%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34] 2.18 [1.65, 2.88] 2.20 [1.09, 4.47] 1.29 [0.82, 2.04]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5 Test for overall effect: 2 1.2.4 48 weeks follow- Cheng 2007	- 16 32 12 21 32 -113 5.31, df = 4 Z = 5.47 (F -up 14	39 25 42 115 <b>251</b> ↓ (P = 0 ○ < 0.00	9 4 9 22 51 .26); I <sup>2</sup> = 0001) 8	38 21 42 115 <b>247</b> 25% 34	3.0% 1.4% 2.9% 7.1% 16.6%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34] 2.18 [1.65, 2.88] 2.20 [1.09, 4.47] 1.29 [0.82, 2.04] 1.69 [1.00, 2.87]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5 Test for overall effect: 2 1.2.4 48 weeks follow: Cheng 2007 Cui 2006	16 32 12 21 32 5.31, df = 4 Z = 5.47 (F -up 14 22	39 25 42 115 <b>251</b> 4 (P = 0 P < 0.00 27 40	9 4 9 22 51 .26); I <sup>2</sup> = 0001) 8 17	38 21 42 115 <b>247</b> 25% 34 40	3.0% 1.4% 2.9% 7.1% 16.6% 2.3% 5.5% 4.2% 4.2%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34] 2.18 [1.65, 2.88] 2.20 [1.09, 4.47] 1.29 [0.82, 2.04] 1.69 [1.00, 2.87] 1.62 [0.98, 2.65]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5 Test for overall effect: 2 1.2.4 48 weeks follow- Cheng 2007 Cui 2006 Li 2009	16 32 12 21 32 5.31, df = 4 Z = 5.47 (F -up 14 22 22	39 25 42 115 <b>251</b> (P = 0 P < 0.00 27 40 40	9 4 9 22 51 .26); I <sup>2</sup> = 0001) 8 17 13	38 21 42 115 <b>247</b> 25% 34 40 40	3.0% 1.4% 2.9% 7.1% 16.6% 2.3% 5.5% 4.2%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34] 2.18 [1.65, 2.88] 2.20 [1.09, 4.47] 1.29 [0.82, 2.04] 1.69 [1.00, 2.87] 1.62 [0.98, 2.65] 2.52 [0.95, 6.66]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5 Test for overall effect: 2 1.2.4 48 weeks follow Cheng 2007 Cui 2006 Li 2009 Nie 2008	16 32 12 21 32 5.31, df = 4 Z = 5.47 (F -up 14 22 22 21	39 25 42 115 <b>251</b> (P = 0 2 < 0.00 27 40 40 33	9 4 9 22 51 .26); I <sup>2</sup> = 0001) 8 17 13 13	38 21 42 115 <b>247</b> 25% 34 40 40 33	3.0% 1.4% 2.9% 7.1% 16.6% 2.3% 5.5% 4.2% 4.2%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34] 2.18 [1.65, 2.88] 2.20 [1.09, 4.47] 1.29 [0.82, 2.04] 1.69 [1.00, 2.87] 1.62 [0.98, 2.65]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5 Test for overall effect: 2 1.2.4 48 weeks follow Cheng 2007 Cui 2006 Li 2009 Nie 2008 Sun 2009	16 32 12 21 32 5.31, df = 4 Z = 5.47 (F -up 14 22 22 21	39 25 42 115 <b>251</b> (P = 0 P < 0.00 27 40 40 33 25	9 4 9 22 51 .26); I <sup>2</sup> = 0001) 8 17 13 13	38 21 42 115 <b>247</b> 25% 34 40 40 33 21	3.0% 1.4% 2.9% 7.1% 16.6% 2.3% 5.5% 4.2% 4.2% 1.4%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34] 2.18 [1.65, 2.88] 2.20 [1.09, 4.47] 1.29 [0.82, 2.04] 1.69 [1.00, 2.87] 1.62 [0.98, 2.65] 2.52 [0.95, 6.66]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5 Test for overall effect: 2 1.2.4 48 weeks follow Cheng 2007 Cui 2006 Li 2009 Nie 2008 Sun 2009 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 2	16 32 12 21 32 5.31, df = 4 Z = 5.47 (F -up 14 22 21 12 21 12 2.52, df = 4	39 25 42 115 <b>251</b> 4 (P = 0 2 < 0.00 27 40 40 33 25 <b>165</b> 4 (P = 0	9 4 9 22 51 .26); l <sup>2</sup> = 0001) 8 17 13 13 4 55 .64); l <sup>2</sup> =	38 21 42 115 <b>247</b> 25% 34 40 40 33 21 <b>168</b>	3.0% 1.4% 2.9% 7.1% 16.6% 2.3% 5.5% 4.2% 4.2% 1.4%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34] 2.18 [1.65, 2.88] 2.20 [1.09, 4.47] 1.29 [0.82, 2.04] 1.69 [1.00, 2.87] 1.62 [0.98, 2.65] 2.52 [0.95, 6.66]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5 Test for overall effect: 2 1.2.4 48 weeks follow: Cheng 2007 Cui 2006 Li 2009 Nie 2008 Sun 2009 Subtotal (95% CI) Total events	16 32 12 21 32 5.31, df = 4 Z = 5.47 (F -up 14 22 21 12 21 12 2.52, df = 4	39 25 42 115 <b>251</b> 4 (P = 0 2 < 0.00 27 40 40 33 25 <b>165</b> 4 (P = 0	9 4 9 22 51 .26); l <sup>2</sup> = 0001) 8 17 13 13 4 55 .64); l <sup>2</sup> =	38 21 42 115 <b>247</b> 25% 34 40 40 33 21 <b>168</b>	3.0% 1.4% 2.9% 7.1% 16.6% 2.3% 5.5% 4.2% 4.2% 1.4%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34] 2.18 [1.65, 2.88] 2.20 [1.09, 4.47] 1.29 [0.82, 2.04] 1.69 [1.00, 2.87] 1.62 [0.98, 2.65] 2.52 [0.95, 6.66]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5 Test for overall effect: 2 1.2.4 48 weeks follow Cheng 2007 Cui 2006 Li 2009 Nie 2008 Sun 2009 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 2	16 32 12 21 32 5.31, df = 4 Z = 5.47 (F -up 14 22 21 12 21 12 2.52, df = 4	39 25 42 115 <b>251</b> 4 (P = 0 2 < 0.00 27 40 40 33 25 <b>165</b> 4 (P = 0	9 4 9 22 51 .26); l <sup>2</sup> = 0001) 8 17 13 13 4 55 .64); l <sup>2</sup> =	38 21 42 115 247 25% 34 40 40 33 21 168	3.0% 1.4% 2.9% 7.1% 16.6% 2.3% 5.5% 4.2% 4.2% 1.4%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34] 2.18 [1.65, 2.88] 2.20 [1.09, 4.47] 1.29 [0.82, 2.04] 1.69 [1.00, 2.87] 1.62 [0.98, 2.65] 2.52 [0.95, 6.66]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5 Test for overall effect: 2 1.2.4 48 weeks follow: Cheng 2007 Cui 2006 Li 2009 Nie 2008 Sun 2009 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 2 Test for overall effect: 2	16 32 12 21 32 5.31, df = 4 Z = 5.47 (F -up 14 22 21 12 21 12 2.52, df = 4	39 25 42 115 251 4 (P = 0 2 < 0.00 27 40 40 33 25 165 4 (P = 0 2 < 0.00	9 4 9 22 51 .26); l <sup>2</sup> = 0001) 8 17 13 13 4 55 .64); l <sup>2</sup> =	38 21 42 115 247 25% 34 40 40 33 21 168	3.0% 1.4% 2.9% 7.1% 16.6% 2.3% 5.5% 4.2% 4.2% 1.4% 17.6%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34] 2.18 [1.65, 2.88] 2.20 [1.09, 4.47] 1.29 [0.82, 2.04] 1.69 [1.00, 2.87] 1.62 [0.98, 2.65] 2.52 [0.95, 6.66] 1.68 [1.30, 2.17]	
Gao 2008 Li 2010 Sun 2009 Yi 2012 Zhao 2006 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 5 Test for overall effect: 2 1.2.4 48 weeks follow: Cheng 2007 Cui 2006 Li 2009 Nie 2008 Sun 2009 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 2 Test for overall effect: 2 Total (95% CI)	16 32 12 21 32 5.31, df = 4 Z = 5.47 (F -up 14 22 21 12 2.52, df = 4 Z = 3.99 (F 513	39 25 42 115 251 4 (P = 0 2 < 0.00 27 40 40 33 25 165 4 (P = 0 2 < 0.00 40 33 25 165 107	9 4 9 22 51 .26); l <sup>2</sup> = 0001) 8 17 13 13 4 55 .64); l <sup>2</sup> = 001) 311	38 21 42 115 247 25% 34 40 40 33 21 168 0% 1012	3.0% 1.4% 2.9% 7.1% 16.6% 5.5% 4.2% 4.2% 1.4% 17.6%	3.46 [1.92, 6.25] 2.52 [0.95, 6.66] 2.33 [1.21, 4.48] 1.45 [0.90, 2.34] 2.18 [1.65, 2.88] 2.20 [1.09, 4.47] 1.29 [0.82, 2.04] 1.69 [1.00, 2.87] 1.62 [0.98, 2.65] 2.52 [0.95, 6.66] 1.68 [1.30, 2.17]	

Figure 2 HBV DNA clearance rates, subgroup analysis of PEG-IFN a vs IFN a 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  $\alpha$  treatment group were significant higher than that in the IFN  $\alpha$  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  $\alpha$  [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  $\alpha$  than in patients treated with IFN  $\alpha$  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 (1.20, 2.06), 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  $\alpha$  [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.

	PEG-IF	Nα	IFN (	ά		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total			Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
1.3.1 24 weeks treatm		Total	LVOINO	Total	mongine	111 11, 1 1X00, 0070 0	
Cui 2006	10	40	6	40	3.7%	1.67 [0.67, 4.15]	
Li 2010	18	39	6	38	3.7%	2.92 [1.30, 6.56]	<b>_</b>
Nie 2008	10	33	3	33	1.8%	3.67 [1.12, 11.96]	
	10	25	5	21	3.3%		
Sun 2009 Zhao 2006	25	115	25	115	3.3% 15.3%	1.68 [0.68, 4.15]	
	25 7	22	25	22	15.3%	1.00 [0.61, 1.63]	
Zhong 2010 Subtotal (95% CI)	1	274	2	269	1.2% 29.2%	3.50 [0.82, 15.01] 1.68 [1.22, 2.31]	▲
Total events	81		47				
Heterogeneity: Chi <sup>2</sup> = 8	3.75, df = 5	5 (P = 0	.12); l <sup>2</sup> =	43%			
Test for overall effect: 2							
	(						
1.3.2 48 weeks treatm	ent						
Cheng 2007	12	27	7	34	3.8%	2.16 [0.99, 4.73]	
Cui 2006	16	40	13	40	8.0%	1.23 [0.68, 2.21]	
Li 2009	13	40	8	40	4.9%	1.63 [0.76, 3.49]	
Nie 2008	13	33	7	33	4.3%	2.43 [1.16, 5.07]	
Sun 2009	14	25	8	21	5.3%	1.47 [0.77, 2.81]	
Zhong 2010	14	23	4	21	2.5%	2.75 [1.03, 7.33]	<b>_</b>
Subtotal (95% CI)	11	187	4	190	2.3%	1.77 [1.32, 2.38]	•
	83	107	47	150	20.070	1.17 [1.02, 2.00]	-
Total events		- (n – o		00/			
Heterogeneity: Chi <sup>2</sup> = 3		•		0%			
Test for overall effect: 2	Z = 3.82 (F	<sup>2</sup> = 0.00	JU1)				
1.3.3 24 weeks follow	-up						
Li 2010	16	39	4	38	2.5%	3.90 [1.43, 10.60]	
Sun 2009	16	25	8	21	5.3%	1.68 [0.90, 3.12]	
Zhao 2006	10	115	16	115	9.8%	1.19 [0.64, 2.19]	
Subtotal (95% CI)	15	179	10	174	17.6%	1.72 [1.15, 2.56]	
Total events	51	175	28		111070		-
Heterogeneity: Chi <sup>2</sup> = 3		) (D - 0		50%			
Test for overall effect: 2		•		50 /6			
	2 – 2.05 (r	0.00	)))				
1.3.4 48 weeks follow	-up						
Cheng 2007	12	27	6	34	3.3%	2.52 [1.09, 5.83]	→
Cui 2006	17	40	14	40	8.6%	1.21 [0.70, 2.12]	
Li 2009	13	40	8	40	4.9%	1.63 [0.76, 3.49]	
Nie 2008	15	33	6	33	3.7%	2.50 [1.11, 5.65]	
Sun 2009	16	25	6	21	4.0%	2.24 [1.07, 4.68]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		165		168	24.4%	1.83 [1.33, 2.52]	
Total events	73		40			• / •	
Heterogeneity: Chi <sup>2</sup> = 3		↓ (P = ∩		0%			
Test for overall effect: 2		•		- /0			
		005		004	400 00/	4 75 14 40 0.003	
Total (95% CI)	~~~	805		801	100.0%	1.75 [1.49, 2.06]	
Total events	288		162				
Heterogeneity: Chi <sup>2</sup> = 2	,	,	<i>,</i> .	= 6%			0.2 0.5 1 2 5
Test for overall effect: 2			,	(B -		o/	Favours IFNa Favours PEG-IFNa
Test for subaroup diffe	rences: Ch	11 <sup>2</sup> = 0.1	15. df = 3	(P = 0.)	98). $I^2 = 0$	%	

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

	PEG-IF	Nα	IFN o	x		Risk Ratio	Risk Ratio
Study or Subgroup					Weight	M-H. Fixed, 95% C	
1.4.1 24 weeks treatm							
Cui 2006	14	40	11	40	5.3%	1.27 [0.66, 2.45]	
Gao 2008	14	30	8	31	3.8%	1.81 [0.89, 3.67]	
Li 2010	18	39	6	38	2.9%	2.92 [1.30, 6.56]	│ —→
Nie 2008	15	33	5	33	2.4%	3.00 [1.23, 7.30]	│ — <b>→</b>
Sun 2009	4	25	2	21	1.0%	1.68 [0.34, 8.28]	
Zhao 2006	26	115	28	115	13.5%	0.93 [0.58, 1.48]	
Zhong 2010	10	22	4	22	1.9%	2.50 [0.92, 6.78]	<u>↓ →</u>
Subtotal (95% CI)	10	304	-	300	30.8%	1.57 [1.20, 2.06]	•
Total events	101		64				
Heterogeneity: Chi <sup>2</sup> = 1		,		43%			
Test for overall effect:	Z = 3.27 (F	<sup>2</sup> = 0.00	JT)				
1.4.2 48 weeks treatm	ient						
Cheng 2007	14	27	9	34	3.8%	1.96 [1.00, 3.82]	
Cui 2006	19	40	16	40	7.7%	1.19 [0.72, 1.96]	
Gao 2008	18	30	11	31	5.2%	1.69 [0.97, 2.95]	
Li 2009	19	40	10	40	4.8%	1.90 [1.01, 3.56]	
Nie 2008	19	33	7	33	3.4%	2.71 [1.32, 5.58]	
Sun 2009	12	25	4	21	2.1%	2.52 [0.95, 6.66]	
Zhong 2010	13	22	5	22	2.4%	2.60 [1.12, 6.05]	
Subtotal (95% CI)		217		221	29.4%	1.88 [1.47, 2.41]	•
Total events	114		62				
Heterogeneity: Chi <sup>2</sup> = 5	5.31, df = 6	6 (P = 0	.51); l <sup>2</sup> = (	0%			
Test for overall effect:							
4.4.2.04 weeks fellow							
1.4.3 24 weeks follow	•		10		4 70/	4 00 14 40 0 501	
Gao 2008	19	30	10	31	4.7%	1.96 [1.10, 3.50]	
Li 2010	19	39	7	38	3.4%	2.64 [1.26, 5.56]	<u>_</u>
Sun 2009	13	25	5	21	2.6%	2.18 [0.93, 5.12]	
Zhao 2006	20	115	16	115	7.7%	1.25 [0.68, 2.29]	
Subtotal (95% CI)		209	00	205	18.4%	1.82 [1.30, 2.55]	
Total events	71		38				
Heterogeneity: Chi <sup>2</sup> = 2		•		0%			
Test for overall effect:	Z = 3.52 (F	<sup>o</sup> = 0.00	004)				
1.4.4 48 weeks follow	-up						
Cheng 2007	15	27	9	34	3.8%	2.10 [1.09, 4.04]	
Cui 2006	20	40	15	40	7.2%	1.33 [0.80, 2.21]	
Li 2009	19	40	10	40	4.8%	1.90 [1.01, 3.56]	
Nie 2008	18	33	6	33	2.9%	3.00 [1.36, 6.60]	<b>→</b>
Sun 2009	13	25	5	21	2.6%	2.18 [0.93, 5.12]	
Subtotal (95% CI)		165		168	21.3%	1.93 [1.44, 2.58]	•
Total events	85		45			• / •	
Heterogeneity: Chi <sup>2</sup> = 3		1 (P = 0		0%			
Test for overall effect:							
Total (95% CIV		895		004	100.0%	1 70 [1 55 0 65]	
Total (95% CI) Total events	371	090	209	034	100.0%	1.78 [1.55, 2.05]	•
Heterogeneity: Chi <sup>2</sup> = 2		22 /D -		= 5%			++
Test for overall effect:				- 0 /0			0.2 0.5 1 2 5
Test for subaroup diffe				(P = ∩	73) l <sup>2</sup> = 0	%	Favours IFNα Favours PEG-IFNo
	. onoca. Ol	1.c	21. ur – J	0.	0	10	

Figure 4 HBeAg clearance rates, subgroup analysis of PEG-IFN a vs IFN a 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  $\alpha$  therapy vs IFN  $\alpha$  therapy. The combined HBsAg clearance rate was 3.8% in PEG-IFN  $\alpha$  treatment group and 1.1% in the IFN  $\alpha$  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  $\alpha$  therapy vs IFN  $\alpha$  therapy on the improvement

of liver fibrosis related biomarkers, included the reduced rate of HA, PC III, IV-c and LN. PEG-IFN  $\alpha$  therapy was more effective than IFN  $\alpha$  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 $\alpha$ + ADV with ADV monotherapy

#### 2.3.1 ALT normalization rates

In comparison of the ADV monotherapy, the combination therapy of PEG-IFN  $\alpha$  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.

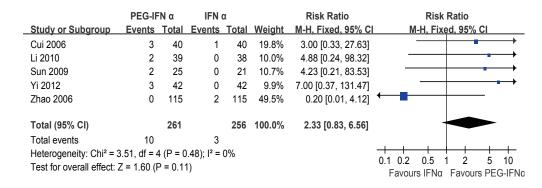


Figure 5 HBsAg clearance rates, subgroup analysis of PEG-IFN a vs IFN a in the treatment of Chinese hepatitis B patients.

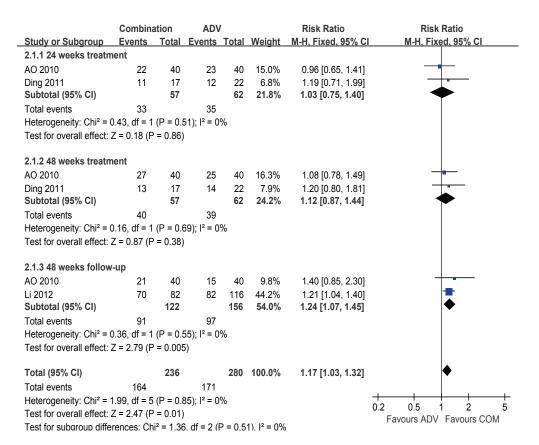


Figure 6 ALT normalization rates, subgroup analysis of PEG-IFN a+ADV vs ADV in the treatment of Chinese hepatitis B patients.

#### 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 followup [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.

	Combina	ation	AD\	,		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI
2.2.1 24 weeks treatn	nent						
AO 2010	17	40	13	40	7.4%	1.31 [0.74, 2.32]	
Ding 2011	12	17	10	22	8.0%	1.55 [0.90, 2.69]	
Subtotal (95% CI)		57		62	15.4%	1.43 [0.96, 2.13]	<b>•</b>
Total events	29		23				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> :	= 0.19, d	df = 1 (P =	= 0.67);	l² = 0%		
Test for overall effect:	Z = 1.76 (P	= 0.08)	)				
2.2.2 48 weeks treatn	nent						
AO 2010	22	40	15	40	9.9%	1.47 [0.90, 2.39]	+
Ding 2011	14	17	11	22	10.5%	1.65 [1.03, 2.64]	
Subtotal (95% CI)		57		62	20.4%	1.56 [1.11, 2.19]	◆
Total events	36		26				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> :	= 0.12, c	df = 1 (P =	= 0.73);	l² = 0%		
Test for overall effect:	Z = 2.56 (P	= 0.01)	)				
2.2.3 48 weeks follow	/-up						
AO 2010	17	40	6	40	3.8%	2.83 [1.25, 6.44]	
Li 2012	77	82	84	116	60.4%	1.30 [1.14, 1.47]	<b></b>
Subtotal (95% CI)		122		156	64.2%	1.77 [0.73, 4.28]	
Total events	94		90				
Heterogeneity: Tau <sup>2</sup> =	0.33; Chi <sup>2</sup> :	= 4.71, c	df = 1 (P =	= 0.03);	l² = 79%		
Test for overall effect:	Z = 1.27 (P	= 0.20)	)				
Total (95% CI)		236		280	100.0%	1.41 [1.20, 1.66]	•
Total events	159		139				
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup> :	= 5.81, d	df = 5 (P =	= 0.33);	l² = 14%		
Test for overall effect:	Z = 4.12 (P	< 0.000	D1)	,.			0.2 0.5 1 2 5 Favours ADV Favours COM
Test for subaroup diffe	erences: Ch	i² = 0.23	3. df = 2 (	P = 0.8	9).  ² = 0%	)	FAVOUIS ADV FAVOUIS COM

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

#### 1203

#### 2.4 Comparison of PEG-IFN a and ETV therapy

Comparison of PEG-IFN  $\alpha$  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  $\alpha$  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  $\alpha$  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  $\alpha$  treatment group, no adverse events were found in the ETV treatment group. All the adverse events were reversible after treatment was stopped.

	Combina		ADV			Risk Ratio		Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fix	ed, 95% Cl
2.3.1 24 weeks treatr	nent							
AO 2010	15	40	6	40	10.0%	2.50 [1.08, 5.79]		
Ding 2011	1	17	1	22	1.5%	1.29 [0.09, 19.23]	•	
Subtotal (95% CI)		57		62	11.5%	2.35 [1.06, 5.21]		
Total events	16		7					
Heterogeneity: Chi <sup>2</sup> =	0.21, df = 1	(P = 0.6	65); l² = 0	%				
Test for overall effect:	Z = 2.10 (P	= 0.04)						
2.3.2 48 weeks treatr	nent							
AO 2010	18	40	7	40	11.7%	2.57 [1.21, 5.47]		
Ding 2011	9	17	3	22	4.4%	3.88 [1.24, 12.18]		
Li 2012	28	82	18	116	24.9%	2.20 [1.31, 3.70]		
Subtotal (95% CI)		139		178	41.0%	2.49 [1.67, 3.71]		
Total events	55		28					
Heterogeneity: Chi <sup>2</sup> =	0.80, df = 2	(P = 0.6	67); l² = 0	%				
Test for overall effect:	Z = 4.46 (P	< 0.000	001)					
2.3.3 48 weeks follov	v-up							
AO 2010	17	40	6	40	10.0%	2.83 [1.25, 6.44]		
Li 2012	38	82	27	116	37.4%	1.99 [1.33, 2.98]		
Subtotal (95% CI)		122		156	47.5%	2.17 [1.51, 3.12]		
Total events	55		33					
Heterogeneity: Chi <sup>2</sup> =	0.58, df = 1	(P = 0.4	45); l² = 0	%				
Test for overall effect:	Z = 4.17 (P	< 0.000	01)					
Total (95% CI)		318		396	100.0%	2.32 [1.80, 2.99]		•
Total events	126		68			-		
Heterogeneity: Chi <sup>2</sup> =	1.88, df = 6	(P = 0.9	93); l² = 0	%			+ +	
Test for overall effect:							0.2 0.5	
Test for subaroup diffe			,	P = 0.8	8).  ² = 0%	)	Favours ADV	/ Favours COM

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

	Combin	ation	ADV	/		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
AO 2010	1	40	0	40	53.2%	3.00 [0.13, 71.51]	
Ding 2011	2	17	0	22	46.8%	6.39 [0.33, 124.91]	
Total (95% CI)		57		62	100.0%	4.58 [0.54, 38.77]	
Total events	3		0				
Heterogeneity: Chi <sup>2</sup> =	0.12, df = 1						
Test for overall effect:	Z = 1.40 (F	= 0.16)	)				0.05 0.2 1 5 20 Favours ADV Favours COM

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

	PEG-IFI	Να	ETV	,		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
4.1.1 serum HBV DNA	A clearance	e rates					
Chen2010	22	34	23	33	100.0%	0.93 [0.66, 1.30]	
Subtotal (95% CI)		34		33	100.0%	0.93 [0.66, 1.30]	•
Total events	22		23				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 0.43 (P	= 0.66	i)				
4.1.2 HBeAg serocon	version						
Chen2010	14	34	4	33	100.0%	3.40 [1.25, 9.26]	
Subtotal (95% CI)	14	34	4		100.0%		
Total events	14	•	4		10010 /0	0110 [1120, 0120]	-
Heterogeneity: Not app			-				
Test for overall effect:		= 0.02	)				
			/				
4.1.3 serum HBeAg c	learance						_
Chen2010	14	34	5	33	100.0%	2.72 [1.10, 6.70]	
Subtotal (95% CI)		34		33	100.0%	2.72 [1.10, 6.70]	-
Total events	14		5				
Heterogeneity: Not app							
Test for overall effect:	Z = 2.17 (P	= 0.03	)				
4.1.4 serum HBsAg c	learance						
Chen2010	4	34	1	33	100.0%	3.88 [0.46, 32.94]	
Subtotal (95% CI)		34		33	100.0%		
Total events	4		1				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 1.24 (P	= 0.21	)				
4.1.5 HBsAg serocon	version						
Chen2010	4	34	0	40	100.00/	10.54 [0.59, 189.08]	<b>→</b>
Subtotal (95% CI)	4	34 34	0			10.54 [0.59, 189.08]	
Total events	4	04	0	40	100.070	10.04 [0.00, 100.00]	
Heterogeneity: Not app			0				
Test for overall effect:		= 0.11	)				
			,				
							0.02 0.1 1 10 50 Favours ETV Favours PEG-IFNα
							FAVOUISEIV FAVOUISFEG-IFINO

Figure 10 Subgroup analysis of serum HBV DNA clearance, HBeAg and HBsAg seroconversion, HBeAg and HBsAg clearance rates between PEG-IFN a 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  $\alpha$  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  $\alpha$  based therapy in the treatment of hepatitis B<sup>[7-10]</sup>. However, the situation in mainland China is that most CHB patients are come from rural areas, the high costs of PEG-IFN  $\alpha$  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  $\alpha$  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  $\alpha$  with other antiviral treatment regimens is needed to examine the beneficial effects of PEG-IFN  $\alpha$ therapy in Chinese patients with hepatitis B.

Our meta-analysis show that in comparison with IFN  $\alpha$ , PEG-IFN  $\alpha$  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  $\alpha$  treatment except for the 24th week of treatment of ALT normalization rate in China. Besides, PEG-IFN  $\alpha$  therapy was more effective than IFN  $\alpha$  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  $\alpha$  is more effective than IFN  $\alpha$  in the treatment of CHB patients in China. Evidence-based studies have demonstrated the efficacy of PEG-IFN  $\alpha$ -2a treatment versus IFN  $\alpha$  in China in 2010<sup>[27]</sup>, our metaanalysis is an undated and extended report on the clinical effectiveness of PEG-IFN  $\alpha$  for the treatment of CHB by adding several new published RCTs recently including PEG-IFN  $\alpha$ -2b therapy and assess the quality by Jadad score.

In the comparison of PEG-IFN  $\alpha$  group versus ETV group for CHB in China, PEG-IFN  $\alpha$  showed superiority in the serological response than ETV, statistically higher rate were found in HBeAg seroconversion rate and HBeAg clearance rates by PEG-IFN  $\alpha$ . Although PEG-IFN  $\alpha$  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  $\alpha$  treatment should be extended to conducive to better efficacy in China.

The situation between the PEG-IFN  $\alpha$  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 a and ADV combination therapy had been reported in western countries<sup>[28-30]</sup>, 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 a 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 a 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 a 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  $\alpha$  treatment relates to HBV genotypes<sup>[31]</sup>. A Meta analysis<sup>[32]</sup> and a pooled analysis of over 1200 patients<sup>[33]</sup> 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  $\alpha$  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 a therapy was more effective than IFN  $\alpha$  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 a was obviously superior to ETV in HBeAg seroconversion and serum HBeAg clearance. The combination therapy of PEG-IFN  $\alpha$  and ADV was effective than ADV monotherapy in ALT normalization, serum HBV DNA clearance and HBeAg seroconversion. PEG-IFN a showed no priority to other treatment regimes in HBsAg clearance. Treatment with PEG-IFN  $\alpha$  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 a combination therapy for CHB patients in China.

### References

- Lam YF, Yuen MF, Seto WK, et al. Current antiviral therapy of chronic hepatitis B: efficacy and safety[J]. Curr Hepat Rep, 2011, 10(4): 235-243.
- Ning LH, Hao J, Liao ZL, et al. A survey on the current trends in the management of hepatitis B in China[J]. Eur J Gastroenterol Hepatol, 2012, 24(8): 884-889.
- Liang X, Bi S, Yang W, et al. Epidemiological serosurvey of hepatitis B in China--declining HBV prevalence due to hepatitis B vaccination[J]. Vaccine, 2009, 27(47): 6550-6557.
- Hadziyannis SJ, Sevastianos V, Rapti I, et al. Sustained responses and loss of HBsAg in HBeAg-negative patients with chronic hepatitis B who stop longterm treatment with adefovir[J]. Gastroenterology, 2012, 143(3): 629-636.
- Feld J, Lee JY, Locarnini S. New targets and possible new therapeutic approaches in the chemotherapy of chronic hepatitis B[J]. Hepatology, 2003, 38(3): 545-553.
- 6. Lok AS, Mcmahon BJ. Chronic hepatitis B: update 2009[J]. Hepatology,

2009, 50(3): 661-662.

- Chan HL, Leung NW, Hui AY, et al. A randomized, controlled trial of combination therapy for chronic hepatitis B: comparing pegylated interferon-alpha2b and lamivudine with lamivudine alone[J]. Ann Intern Med, 2005, 142(4): 240-250.
- Janssen HL, van Zonneveld M, Senturk H, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial[J]. Lancet, 2005, 365(9454): 123-129.
- Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B[J]. N Engl J Med, 2005, 352(26): 2682-2695.
- Cooksley WG, Piratvisuth T, Lee SD, et al. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B[J]. J Viral Hepat, 2003, 10(4): 298-305.
- Sun J, Hou JL. Management of chronic hepatitis B: experience from China[J]. J Viral Hepat, 2010, 17(Suppl 1): 10-17.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?[J]. Control Clin Trials, 1996, 17(1): 1-12.
- 孙萍, 蒲涛. 聚乙二醇干扰素α-2a治疗HBeAg阳性的慢性乙肝的临床研究[J]. 中国当代医药, 2009, 16(9): 39-40.
   SUN Ping, PU Tao. Clinical research of the pegylated interferon α-2a for the treatment of HBeAg-positive chronic hepatitis B[J]. China Modern Medicine, 2009, 16(9): 39-40.
- 14. 李志勤, 孙长宇, 武淑环, 等. 聚乙二醇干扰素a-2a治疗HBeAg阳 性慢乙肝疗效评价[J]. 医药论坛杂志, 2010, 31(2): 51-53.
  LI Zhiqin, SUN Changyu, WU Shuhuan, et al. Efficacy evaluate of pegylated interferon a-2a treatment for HBeAg-positive chronic hepatitis B[J]. Journal of Medical Forum, 2010, 31(2): 51-53.
- 崔建军, 范平, 蒋小玲, 等. 聚乙二醇干扰素α-2a治疗HBeAg阳性 慢性乙型肝炎的疗效和安全性[J]. 中华实验和临床病毒学杂 志, 2006, 20(12): 331-333.

CUI Jianjun, FAN Ping, JIANG Xiaoling, et al. The efficacy and safety of pegylated interferon  $\alpha$ -2a therapy for HBeAg-positive chronic hepatitis B[J]. Journal of Experimental and clinical Virology, 2006, 20(12): 331-333.

- 厉景南,李朝霞,施云珍,等.聚乙二醇化干扰素α-2a和干扰素α-2a 治疗e抗原阳性慢性乙型肝炎[J].中国医刊,2009,44(7):35-36.
   LI Jingnan, LI Zhaoxia, SHI Yunzhen, et al. Pegylated interferon α-2a and interferon α-2a therapy for HBeAg-positive chronic hepatitis B[J]. Chinese Journal of Medicine, 2009, 44(7):35-36.
- 17. 衣展华,陈俊飞,丁锷,等.聚乙二醇化干扰素α-2a治疗HBeAg阳 性慢性乙型肝炎疗效观察[J]. 肝脏, 2012, 17(1): 39-42.
  YI Zhanhua, CHEN Junfei, DING E, et al. Efficacy of pegylated interferon α-2a therapy for HBeAg-positive chronic hepatitis B[J]. Liver, 2012, 17(1): 39-42.
- 程乾刚, 赵海龙. 聚乙二醇化干扰素α-2a治疗慢性乙型肝炎的疗效与安全性[J]. 临床肝胆病杂志, 2007, 23(6): 424-426.
   CHENG Qiangang, ZHAO Haihong. The efficacy and safety of pegylated interferon α-2a therapy for HBeAg-positive chronic hepatitis

B[J]. Clinical Hepatology, 2007, 23(6): 424-426.

- 钟少龙. 聚乙二醇化干扰素α-2a治疗慢性乙型肝炎的临床观察
   [J]. 中国医药指南, 2010, 8(5): 71-72.
   ZHONG Shaolong. Efficacy of pegylated interferon α-2a therapy for HBeAg-positive chronic hepatitis B[J]. Guide to Chinese Medicine, 2010, 8(5): 71-72.
- > 聂仁丽,杨文东,李爱茜.聚乙二醇化干扰素α-2a治疗慢性乙型 肝炎的临床观察[J]. 医学临床研究, 2008, 25(8):1461-1463.
   NIE Renli, YANG Wendong, LI Aiqian. Clinical observation of pegylated interferon α-2a therapy for HBeAg-positive chronic hepatitis B[J]. Journal of Clinical Reseach, 2008, 25(8): 1461-1463.
- 赵宏, 斯崇文, 魏来, 等. 聚乙二醇化干扰素a-2b与干扰素a-2b治 疗e抗原阳性慢性乙型肝炎的疗效和安全性的随机对照多中心 研究[J]. 中华肝脏病杂志, 2006, 14(5): 323-326.
   ZHAO Hong, SI Chongwen, WEI Lai, et al. A multicenter, randomized, open-label study on the safety and effectiveness of pegylated interferon alpha-2b and interferon alpha-2b in treating HBeAg positive chronic hepatitis B patients[J]. Chinese Journal of Hepatology, 2006, 14(5): 323-326.
- 高胜利,吴建成,陈祖涛,等.聚乙二醇干扰素a-2a治疗慢性乙型 肝炎疗效观察[J].苏州大学学报:医学版,2008,28(1):136-137.
   GAO Shengli, WU Jiancheng, CHEN Zutao, et al. Clinical observation of pegylated interferon a-2a therapy for chronic hepatitis B patients[J].
   Suzhou University Journal. Medical Science, 2008, 28(1): 136-137.
- 敖飞健, 马为民, 周伯平, 等. 聚乙二醇干扰素α-2a、阿德福韦酯 单用及联合应用治疗HBeAg阳性慢性乙型肝炎患者的疗效及 安全性比较[J]. 中华传染病杂志, 2010, 28(4): 214-217.
   AO Feijian, MA Weimin, ZHOU Boping, et al. The efficacy and safety of adefovir dipivoxil, pegylated interferon α-2a monotherapy and combination therapy for HBeAg-positive chronic hepatitis B patients[J]. Journal of Infectious Disease, 2010, 28(4): 214-217.
- 24. 丁继光, 李文斌, 孙庆丰, 等. 聚乙二醇干扰素a-2a、阿德福韦酯 单用及联合应用治疗HBeAg阳性慢性乙型肝炎患者的疗效观 察[R]. 浙江: 浙江省医学会, 2010.
  DING Jiguang, LI Wenbin, SUN Qingfeng, et al. Efficacy of

adefovir dipivoxil and pegylated interferon α-2a monotherapy and its combination therapy for HBeAg-positive chronic hepatitis B patients[R]. Zhe Jiang: Zhejiang Medicine Association, 2010.

- 李孝楼,高海冰.阿德福韦联合聚乙二醇干扰素α-2b治疗性慢性 乙型肝炎的临床疗效观察[J]. 医学检验, 2012, 8(12):69-70.
   LI Xiaolou, GAO Haibin. Clinical efficacy of adefovir dipivoxil and pegylated interferon α-2b combination therapy for HBeAg-positive chronic hepatitis B[J]. Medical Laboratory Science, 2012, 8(12): 69-70.
- 陈学福,陈小苹,陈文莉,等.聚乙二醇干扰素α-2a与恩替卡韦治 疗慢性乙型肝炎的对照研究[J].中华传染病杂志,2010,28(1):
   42-46.

 $\label{eq:chen} \begin{array}{l} \mbox{CHEN Xuefu, CHEN Xiaoping, CHEN Wenli, et al. Control research} \\ \mbox{of pegylated interferon $\alpha$-2a and entecavir therapy for chronic hepatitis} \\ \mbox{B[J]. Journal of Infectious Disease, 2010, 28(1): 42-46.} \end{array}$ 

27. Yu HB, Liu EQ, Lu SM, et al. Treatment with peginterferon

versus interferon in Chinese patients with hepatitis B[J]. Biomed Pharmacother, 2010, 64(8): 559-564.

- 28. Wursthorn K, Lutgehetmann M, Dandri M, et al. Peginterferon alpha-2b plus adefovir induce strong cccDNA decline and HBsAg reduction in patients with chronic hepatitis B[J]. Hepatology, 2006, 44(3): 675-684.
- 29. Jones J, Shepherd J, Baxter L, et al. Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation[J]. Health Technol Assess, 2009, 13(35): 1-172.
- 30. Takeda A, Jones J, Shepherd J, et al. A systematic review and economic evaluation of adefovir dipivoxil and pegylated interferon-alpha-2a for the treatment of chronic hepatitis B[J]. J Viral Hepat, 2007, 14(2): 75-88.
- 31. Raimondi S, Maisonneuve P, Bruno S, et al. Is response to antiviral treatment influenced by hepatitis B virus genotype?[J]. J Hepatol, 2010, 52(3): 441-449.
- 32. Wiegand J, Hasenclever D, Tillmann HL. Should treatment of hepatitis B depend on hepatitis B virus genotypes? A hypothesis generated from an explorative analysis of published evidence[J]. Antivir Ther, 2008, 13(2): 211-220.

33. Erhardt A, Ludwig AD, Brunetto M, et al. HBV genotype are the strongest predictors of response to interferon-alfa treatment: multivariate evaluation in 1229 hepatitis B patients[J]. Hepatology, 2008, 48(Suppl): 700A.

#### (Edited by GUO Zheng)

本文引用: 邓珍珍, 王春江, 李佐军, 李兵, 刘世坤. 聚乙二醇干扰 素a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[J]. 中南大学学报:医学版, 2013, 38(12): 1193-1207. DOI:10.3969/j.issn.1672-7347.2013.12.001

Cite this article as: DENG Zhenzhen, WANG Chunjiang, LI Zuojun, LI Bing, LIU Shikun. Peginterferon alpha versus other antiviral regimes for Chinese HBeAg-positive chronic hepatitis B patients[J]. Journal of Central South University. Medical Science, 2013, 38(12): 1193-1207. DOI:10.3969/j.issn.1672-7347.2013.12.001

		以下常用词汇, 允许直接使用缩	与,即自次:		
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	为素法 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 <sub>2</sub>
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	ТГ	一氧化氮合酶	NOS
动脉血二氧化碳分压	PaCO <sub>2</sub>	凝血酶原时间	PT	乙二胺四乙酸	EDTA
动脉血氧分压	PaO <sub>2</sub>	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 <sub>2</sub> O	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 - кB	NF-ĸB	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				

## 本刊常用词汇英文缩写表