Original Article

A Potential Functional Cure in Chinese HBeAg-negative Chronic Hepatitis B Patients Treated with Peg-interferon Alpha-2a

Xinyue Chen[#1], Qianguo Mao[#2], Yao Xie[#3], Xiaoguang Dou[4], Qing Xie[5], Jifang Sheng[6], Zhiliang Gao[7], Xiaoling Zhou[8], Yingxia Liu[9], Huanwei Zheng[10], Shuqin Zhang[11], Shibo Li[12], Fusheng Zhu[13], Yuqin Xu[14], Mingxiang Zhang[15], Yaoren Hu[16], Xiaoping Chen[17], Yan Huang[18], Hong Ren*[19] and Jidong Jia*[20]

[1]*International Medicine Ward, Beijing YouAn Hospital, Capital Medical University, Beijing, China;* [2]*Department of Infectious Diseases, Xiamen Hospital of Traditional Chinese Medicine, Xiamen, Fujian, China;* [3]*Department of Liver Disease, Beijing Ditan Hospital, Capital Medical University, Beijing, China;* [4]*Department of Infectious Diseases, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China;* [5]*Department of Infectious Diseases, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China;* [6]*Department of Infectious Diseases, The First Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang, China;* [7]*Department of Infectious Diseases, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China;* [8]*Department of Gastroenterology, Liuzhou Traditional Chinese Medical Hospital, Liuzhou, Guangxi, China;* [9]*Department of Infectious Diseases, Shenzhen Third People's Hospital, Shenzhen, Guangdong, China;* [10]*Department of Infectious Diseases, The Fifth Hospital of Shijiazhuang, Shijiazhuang, Hebei, China;* [11]*Department of Infectious Diseases, Hepatology Hospital of Jilin Province, Changchun, Jilin, China;* [12]Department of Infectious Diseases, Zhoushan Hospital of Zhejiang Province, Zhoushan, Zhejiang, China; [13]*Department of Infectious Diseases, General Hospital of Dagang Oilfield, Tianjin, China;* [14]Department of Infectious Diseases, The 211 Hospital of People's Liberation Army, Harbin, Heilongjiang, China; [15]*Department of Integrated Traditional and Western Medicine on Liver Diseases, The Sixth People's Hospital of Shenyang, Shenyang, Liaoning, China;* [16]Department of Liver Disease, Ningbo No. 2 Hospital of Zhejiang Province, Ningbo, Zhejiang, China; [17]*Department of Infectious Diseases, Guangdong General Hospital, Guangzhou, Guangdong, China;* [18]Department of Medical Science, Shanghai Roche Pharmaceuticals Ltd., Shanghai, China; [19]*Department of Infectious Diseases, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China;* [20]Department of Liver Disease, Beijing Friendship Hospital, Capital Medical University, Beijing, China

Abstract

Background and Aims: Data are limited on the use of pegylated-interferon alpha-2a (peg-IFNα) in Chinese patients with chronic hepatitis B virus (HBV) infection (CHB). We evaluated the effectiveness and safety of peg-IFNα in Chinese patients with hepatitis B envelope antigen-negative CHB in routine clinical practice. ***Methods:*** In this prospective, multicenter, observational, non-interventional cohort study, patients were assessed for up to 1 year after peg-IFNα treatment cessation. Treating physicians established the dosing and treatment duration according to Chinese clinical practice. Effectiveness of peg-IFNα treatment was measured by the percentage of: patients with HBV DNA <2000 IU/mL and loss of hepatitis B surface antigen (commonly known as HBsAg); HBV DNA level at end of treatment (EOT), and 6 months and 1 year posttreatment; and time course change in quantitative HBV DNA and HBsAg. ***Results:*** At EOT, 6 months posttreatment, and 1 year posttreatment, the percentage of patients with HBV DNA <2000 IU/mL was 90.0%, 81.8%, and 82.2%, and that of patients with HBsAg loss was 6.5%, 9.4%, and 9.5%, respectively. The HBV DNA level decreased from 5.61 log IU/mL at baseline to 2.48 log IU/mL at EOT and 2.67 log IU/mL at 1 year posttreatment. The HBsAg level decreased from 3.08 log IU/mL at baseline to 2.24 log IU/mL at EOT and 2.10 log IU/mL at 1 year posttreatment. The incidence of adverse events was 52.0%. ***Conclusions:*** Peg-IFNα has the potential to provide functional cure (HBsAg loss) for CHB and is well tolerated in hepatitis B envelope antigen-negative CHB patients in routine clinical practice in China. ***Clinical Trial Registration:*** ClinicalTrials.gov (NCT01730508).

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Keywords: Chronic hepatitis B; Prospective studies; Observational study; Interferon alpha.

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; EOT, end of treatment; FAS-MSC, full analysis set of those who meet selection criteria; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NUC, nucleoside analogue; peg-IFNα, pegylated-interferon alpha-2a; SD, standard deviation; ULN, upper limit of normal.

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[#]These authors contributed equally to this study.

***Correspondence to:** Hong Ren, Department of Infectious Diseases, The Second Affiliated Hospital of Chongqing Medical University, No. 76, Linjiang Road, Yuzhong District, Chongqing 400010, China. Tel: +86-13983888786, Fax: +86-23-63711527, E-mail: renhong0531@vip.sina.com; Jidong Jia, Department of Liver Disease, Beijing Friendship Hospital, Capital Medical University, No. 95 Yong'an Road, Xicheng District, Beijing 100069, China. Tel: +86-13501378269, Fax: +86-10-62704289, E-mail: jiamd@263.net

Introduction

According to the World Health Organization Global Hepatitis Report in 2017, 257 million people worldwide were living with chronic hepatitis B virus (HBV) infection (CHB),[1] among whom one third (86 million) were located in China.[2] In China, surveys conducted in 2006 and 2014 showed a decreasing trend in hepatitis B surface antigen (HBsAg) prevalence after the start of a vaccination program in 1992.[3] However, in 2016, the prevalence of HBsAg was reported to be relatively high, namely 6.0% in men aged 21–49 years in rural China[4] and 6.1% in Northeastern China.[5] Among HBsAg-positive individuals, the lifetime relative risk for hepatocellular carcinoma was reported to be 15- to 20-fold higher compared with that of HBsAg-negative individuals,[6] and the risk of hepatocellular carcinoma significantly decreased in CHB patients with HBsAg clearance.[7]

Hepatitis B envelope antigen (HBeAg)-negative CHB represents a late phase in the natural history of CHB that develops immediately after HBeAg seroconversion or after a long inactive chronic hepatitis B virus carrier phase.[8,9] HBeAg-negative CHB patients often require treatment because spontaneous remission rarely occurs, and these patients have more advanced liver disease compared with HBeAg-positive patients.[8–10]

The therapeutic goal of CHB is to achieve a "functional" cure, which is characterized by sustained HBsAg loss, but is almost impossible to achieve with nucleoside analogues (NUCs) (including entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide).[11] The efficacy of pegylated-interferon alpha (peg-IFNα) in terms of HBsAg clearance and/or improvement in sustained off-treatment virologic response was shown in several interventional multi-national studies in Caucasian patients with HBeAg-negative CHB.[9,12–15] In a phase 3 study investigating 177 HBeAg-negative CHB patients who received peg-IFNα in combination with lamivudine for 48 weeks, HBsAg clearance was achieved by 5% of patients at 1 year posttreatment.[9,16] This rate increased to 12% at 5 years posttreatment.[16] Among patients with HBV DNA <2000 IU/mL at 1 year posttreatment, 28% achieved HBsAg loss at 5 years posttreatment.[16] The PegBeLiver study demonstrated that extended treatment (96 weeks) with peg-IFNα was well tolerated, and significantly improved sustained response rates measured by HBsAg loss in HBeAg-negative patients predominantly infected with HBV genotype D (6%, 1 year posttreatment).[12] In a study on a small sample of Chinese HBeAg-negative patients, a significantly greater HBsAg clearance rate at 48 weeks posttreatment was reported among those who received extended treatment with peg-IFNα (72 weeks) compared with standard treatment (48 weeks) (35.7% vs. 10.5%, respectively; $p < 0.05$).[17]

The dominant HBV genotypes are B and C in Asia and A and D in Europe. As responses to interferon treatment have been found to vary depending on the HBV genotype,[18] and these genotypes follow a geographical distribution, it is important to evaluate Asian patients separately. Although HBeAg-negative CHB is less common in China than in Europe, the incidence of HBeAg-negative disease has increased in China.[19] Considering the limited data on peg-IFNα in Asian/Chinese patient populations, the difference in response to treatment based on the dominant HBV genotype and the increasing incidence of HBeAg-negative disease in China, the present study aimed to evaluate the effectiveness and safety of peg-IFNα in Chinese patients with HBeAg-negative CHB in routine clinical practice.

Methods

Study design and patients

This was a prospective, observational, noninterventional cohort study. Dosing and treatment duration were determined at the discretion of the investigator and reflect actual Chinese clinical practice. Patients were followed up for 1 year after treatment cessation. Data on treatment outcomes (i.e. HBV DNA, HBsAg, quantitative HBsAg, hepatitis B surface antibody, and alanine aminotransferase [ALT]) were collected from medical records and documented in electronic case report forms.

HBeAg-negative CHB patients from 79 study sites in China (Supplemental Table 1) who received peg-IFNα therapy from November 2012 to April 2015 were consecutively enrolled. The key eligibility criteria included serum ALT >upper limit of normal (ULN) but ≤10 × ULN, and HBV DNA ≥2000 IU/mL according to Chinese peg-IFNα-2a labeling and HBV clinical practice guidelines.[20] Those who did not meet the eligibility criteria were excluded from the effectiveness analysis.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent in writing was obtained from all patients included in the study. This study was registered at ClinicalTrials.gov (NCT01730508).

End-points

The following effectiveness end-points were evaluated as percentage of patients with: HBV DNA <2000 IU/mL, <400 IU/mL, and <200 IU/ml; HBsAg <10 IU/mL, <100 IU/mL, and <1000 IU/mL; HBsAg loss; and HBsAg seroconversion at end of treatment (EOT), 6 months posttreatment, and 1 year posttreatment. The time course change in quantitative HBV DNA and HBsAg during the observation period and baseline and on-treatment predictors of response were also evaluated. An analysis of predefined subgroups was performed according to treatment pattern (peg-IFNα monotherapy, NUC add-on during peg-IFNα treatment, and NUC add-on during follow-up), baseline ALT level (≤2, >2 and ≤5, and >5 ULN), age (<35 and ≥35 years), treatment duration (48, 72, and 96 weeks), and early treatment response (HBV DNA decline >2 log plus ALT increase at week 12 and HBV DNA decline ≤2 log or no ALT increase at week 12) in patients who received Peg-IFNα monotherapy. For safety, reported adverse events (AEs) and laboratory data were evaluated.

Statistical analysis

The full analysis set (FAS) was defined as the subjects who underwent at least one dose of peg-IFNα treatment and was used for the safety analysis. The FAS of those who meet selection criteria (FAS-MSC) was defined as FAS subjects who met all the selection criteria of this study, and was used for the effectiveness analysis. Descriptive statistics were used for baseline demographic and clinical characteristics, with *n* (%) for categorical variables and mean ± standard deviation (SD) for continuous variables. Statistical tests and 95% confidence

intervals (CIs) were two-sided. The significance level was set at $p \leq 0.05$. The response rate of HBV DNA suppression, ALT normalization, HBsAg loss, and seroconversion was calculated, and the exact 95% (two-sided) CIs from the binomial distribution were provided. The effectiveness analyses were performed in patients with measurements at the corresponding time point. The statistical software used for the statistical analysis was SAS® (software package version 9.2; SAS Inc., Cary, NC, USA).

Results

Patients

The patient population is shown in Fig. 1. In total, 930 patients from 79 sites were enrolled and treated with at least one dose of peg-IFNα, and were included in the FAS (safety analysis). However, 268 patients did not meet the eligibility criteria, so only 662 patients were included in the FAS-MSC (effectiveness analysis). Of the 662 patients in the FAS-MSC, 33.7% did not complete the 1 year follow-up (Fig. 1). A total of 476 (71.9%) patients completed 48 weeks of treatment, 167 (25.2%) completed 72 weeks of treatment, and 71 (10.7%) completed 96 weeks of treatment. Among patients in the FAS-MSC, the most common treatment pattern was peg-IFNα monotherapy (80.4%), followed by NUC add-on during peg-IFNα treatment (14.7%), and NUC add-on during follow-up (5.0%) (Fig. 1). The number of patients with each measurement at each time point is shown in Supplemental Table 2.

The baseline demographic and clinical characteristics in all patients who met eligibility criteria are shown in Table 1. The mean age was 37.9 years and most patients were male (81.0%). The mean HBV DNA and HBsAg levels were 5.6 log IU/mL and 3.1 log IU/mL, respectively.

Among patients with known HBV genotype, genotypes B and C were the dominant genotypes.

Effectiveness

Fig. 2A shows the percentage of patients with HBV DNA <2000 IU/mL, <400 IU/mL, and <200 IU/mL, that of patients with a combined response (HBV DNA <2000 IU/mL and ALT normalization), and that of patients with HBsAg loss and HBsAg seroconversion at EOT, 6 months posttreatment, and 1 year posttreatment. At 1 year posttreatment, the percentage of patients with HBV DNA <2000 IU/mL was 82.2% (95% CI 77.4, 86.3) in FAS-MSC subjects with available results at 1 year posttreatment. The percentage of patients with suppression of HBV DNA to <2000 IU/mL was 90.0% at EOT and 81.8% at 6 months posttreatment. The percentage of patients with suppression of HBV DNA to <400 IU/mL and <200 IU/mL at EOT, 6 months posttreatment, and 1 year posttreatment ranged between 35.6% and 45.5%. The percentage of patients with a combined response (HBV DNA <2000 IU/mL and ALT normalization) increased from 51.0% at EOT to 71.6% and 73.4%, respectively, at 6 months and 1 year posttreatment. The percentage of patients with HBsAg loss was 6.5% at EOT, 9.4% at 6 months posttreatment, and 9.5% at 1-year posttreatment; the percentage of patients with HBsAg seroconversion was 5.2% at EOT, 7.6% at 6 months posttreatment, and 7.1% at 1 year posttreatment.

The change of HBsAg category throughout the observation period is shown in Fig. 2B. The percentage of patients with

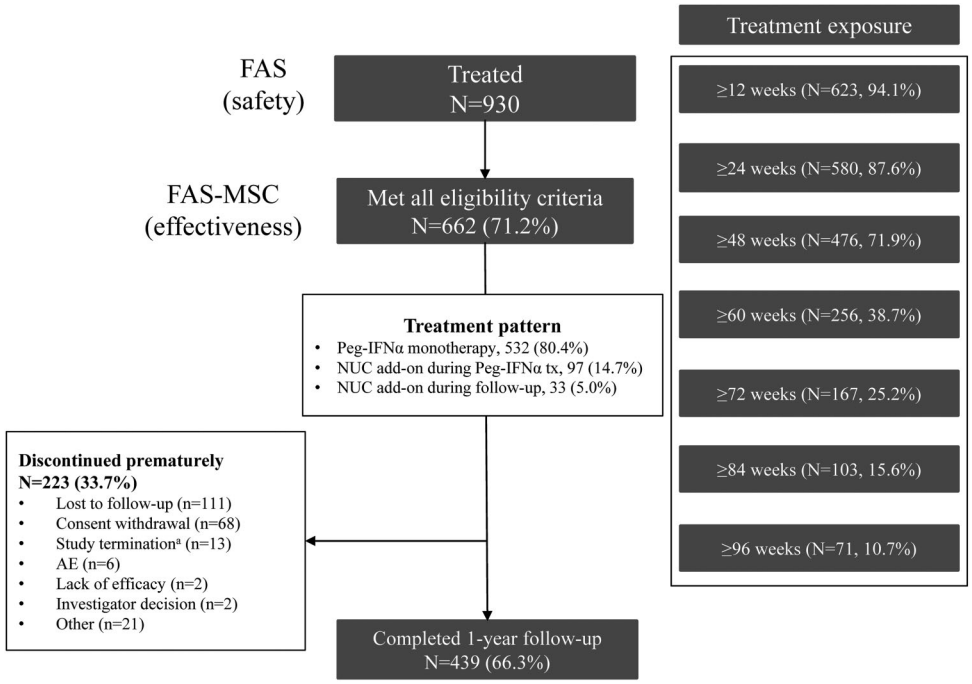

Fig. 1. Patient disposition. The predefined date to stop data collection was at 1 year after the last enrolled patient completed the treatment. At the final cut-off (date to stop data collection), 13 patients who received prolonged treatment were still within the 1 year follow-up window.

Abbreviations: AE, adverse event; FAS, full analysis set; FAS-MSC, full analysis set of those who meet selection criteria; NUC, nucleoside analogue; peg-IFNα, pegylated-interferon alpha-2a; tx, treatment.

Table 1. Baseline demographic and clinical characteristics in all patients and by subgroups

		Treatment pattern			ALT level*			Age*		Treatment duration*			Treatment response*	
	Total (*n* = 662)	Peg-IFNα monotherapy (*n* = 532)	NUC add-on during peg-IFNα treatment (*n* = 97)	NUC add-on during follow-up (*n* = 33)	≤2 ULN (*n* = 184)	>2 and ≤5 ULN (*n* = 256)	>5 ULN (*n* = 92)	<35 years (*n* = 209)	≥35 years (*n* = 323)	48 weeks (*n* = 249)	72 weeks (*n* = 111)	96 weeks (*n* = 37)	HBV DNA decline >2 log plus ALT increase at week 12 (*n* = 48)	HBV DNA decline ≤2 log or no ALT increase at week 12 (*n* = 338)
Age in years	37.9 ± 9.4	37.6 ± 9.3	39.4 ± 9.6	37.6 ± 9.9	38.3 ± 9.2	37.0 ± 9.4	37.7 ± 9.2	28.3 ± 4.1	43.6 ± 6.2	37.6 ± 8.9	38.6 ± 9.7	35.6 ± 7.6	38.5 ± 7.0	37.4 ± 9.4
Male	536 (81.0)	426 (80.1)	83 (85.6)	27 (81.8)	154 (83.7)	205 (80.1)	67 (72.8)	157 (75.1)	269 (83.3)	187 (75.1)	94 (84.7)	32 (86.5)	37 (77.1)	273 (80.8)
HBV DNA as log IU/m	5.6 ± 1.2	5.6 ± 1.2	5.7 ± 1.2	6.0 ± 1.3	5.2 ± 1.1	5.7 ± 1.2	5.9 ± 1.2	5.7 ± 1.3	5.5 ± 1.1	5.6 ± 1.2	5.5 ± 1.2	5.6 ± 1.1	5.5 ± 1.0	5.7 ± 1.2
ALT, ULN	3.2 ± 2.0	3.2 ± 2.0	2.7 ± 1.7	3.7 ± 2.3	1.5 ± 0.3	3.1 ± 0.8	6.9 ± 1.3	3.2 ± 1.8	3.2 ± 2.1	3.3 ± 2.0	3.2 ± 2.2	3.5 ± 2.3	1.7 ± 0.7	3.5 ± 2.1
HBsAg as log IU/mL	3.1 ± 0.8	3.0 ± 0.8	3.3 ± 0.6	3.2 ± 0.8	2.9 ± 0.9	3.1 ± 0.8	3.0 ± 0.8	3.1 ± 0.9	3.0 ± 0.7	3.1 ± 0.9	3.0 ± 0.8	3.0 ± 0.7	2.9 ± 0.9	3.1 ± 0.8
Known hepatitis B disease course in months	117.5 ± 99.1	116.9 ± 100.9	125.4 ± 90.8	104.7 ± 93.8	121.2 ± 99.1	107.9 ± 98.2	133.1 ± 110.3	92.8 ± 82.0	132.5 ± 108.8	120.3 ± 106.6	117.8 ± 90.4	119.4 ± 108.2	138.2 ± 86.3	121.6 ± 106.4
HBV genotype														
A/E/F/G	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B	32 (4.8)	25 (4.7)	6 (6.2)	1 (3.0)	4 (2.2)	17 (6.6)	4 (4.3)	9 (4.3)	16 (5.0)	4 (1.6)	12 (10.8)	2 (5.4)	1 (2.1)	18 (5.3)
C	46 (6.9)	34 (6.4)	11 (11.3)	1 (3.0)	9 (4.9)	20 (7.8)	5 (5.4)	15 (7.2)	19 (5.9)	10 (4.0)	10 (9.0)	5 (13.5)	3 (6.3)	19 (5.6)
D	1 (0.2)	1 (0.2)	0	0	0	0	1 (1.1)	1 (0.5)	0	0	0	0	0	0
H	1 (0.2)	1 (0.2)	0	0	0	0	1 (1.1)	0	1 (0.3)	0	1 (0.9)	0	0	0
Unknown	577 (87.2)	467 (87.8)	79 (81.4)	31 (93.9)	167 (90.8)	219 (85.5)	81 (88.0)	183 (87.6)	284 (87.9)	234 (94.0)	87 (78.4)	30 (81.1)	43 (89.6)	300 (88.8)
Others	5 (0.8)	4 (0.8)	1 (1.0)	0	4 (2.2)	0	0	1 (0.5)	3 (0.9)	1 (0.4)	1 (0.9)	0	1 (2.1)	1 (0.3)
With anti-HBV history	147 (22.2)	101 (19.0)	43 (44.3)	3 (9.1)	34 (18.5)	49 (19.1)	18 (19.6)	38 (18.2)	63 (19.5)	49 (19.7)	23 (20.7)	6 (16.2)	7 (14.6)	67 (19.8)

Data are shown as *n* (%) or mean ± SD. *In patients who received peg-IFNα monotherapy.

Abbreviations: ALT, alanine aminotransferase; FAS-MSC, analysis set of those who meet selection criteria; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NUC, nucleoside analog; peg-IFNα, pegylated-interferon alpha-2a; ULN, upper limit of normal.

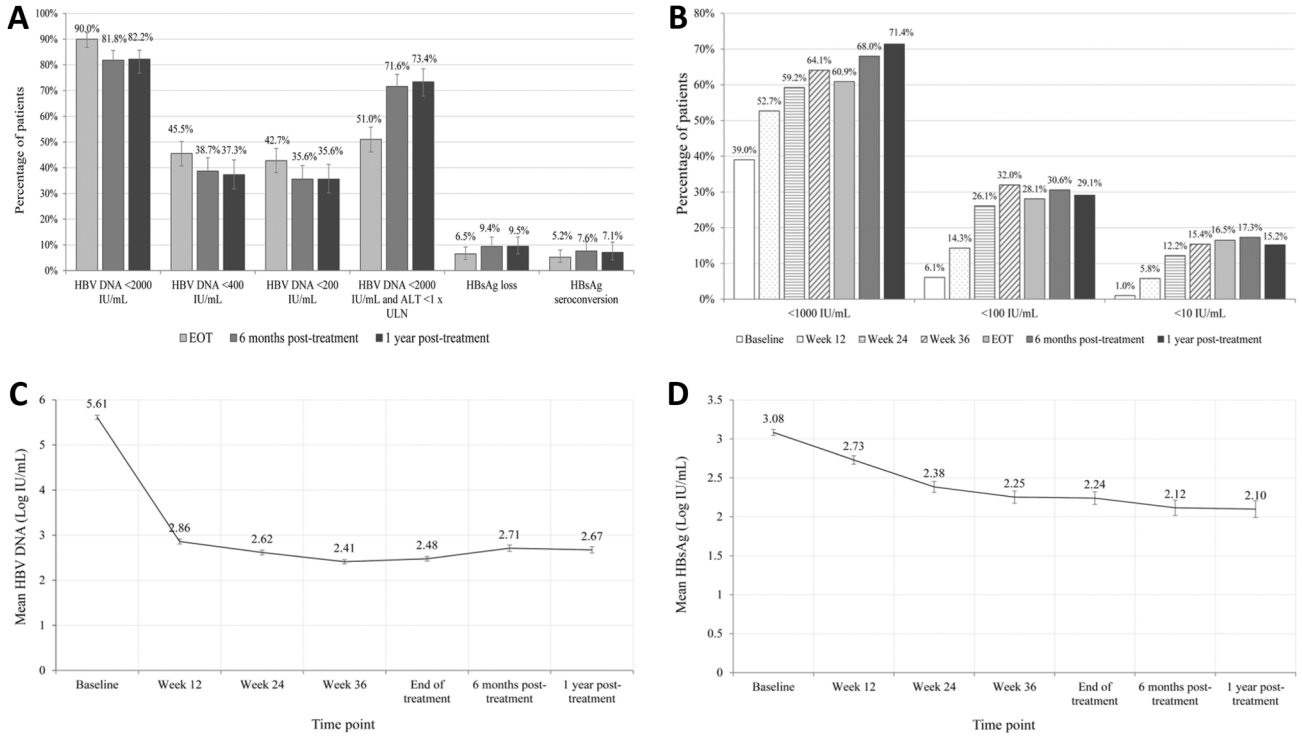

Fig. 2. Percentage of patients with HBV DNA <2000 IU/mL, <400 IU/mL, and <200 IU/mL, that of patients with a combined response (HBV DNA <2000 IU/mL and ALT normalization), and that of patients with HBsAg loss and HBsAg seroconversion at EOT, 6 months posttreatment, and 1 year posttreatment (A), as well as changes in HBsAg category (B), time course change of mean HBV DNA (C), and time course change of mean HBsAg (D). The error bars in 2A indicate 95% confidence intervals and those in C and D indicate standard errors. The mean values in C and D were calculated using the data of the FAS-MSC.

Abbreviations: ALT, alanine aminotransferase; EOT, end of treatment; FAS-MSC, full analysis set of those who met the selection criteria; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ULN, upper limit of normal.

HBsAg level <1000 IU/mL increased from 39.0% at baseline to 71.4% at 1 year posttreatment. That of patients with HBsAg level <100 IU/mL increased from 6.1% at baseline to 29.1% at 1 year posttreatment, and that of patients with HBsAg level <10 IU/mL increased from 1.0% at baseline to 15.2% at 1 year posttreatment.

The time course change of HBV DNA and HBsAg level throughout the study period is shown in Fig. 2C and 2D, respectively. The HBV DNA level decreased from 5.61 log IU/mL at baseline to 2.48 log IU/mL at EOT and 2.67 log IU/mL at 1 year posttreatment. The HBsAg level decreased from 3.08 log IU/mL at baseline to 2.24 log IU/mL at EOT and 2.10 log IU/mL at 1 year posttreatment.

Predictors of response

We assessed baseline predictors of HBV DNA <2000 IU/mL at the end of a 1-year follow-up period, including sex, age, body mass index, method of HBV transmission, hepatitis B disease course, anti-HBV history, HBV genotype, HBV DNA level, HBsAg level, and ALT level. However, univariate and multivariate logistic regression analyses did not reveal any statistically significant relationships (data not shown).

Similarly, early HBV DNA and HBsAg response were not found to be significant predictors of HBV DNA suppression at 1 year posttreatment. The receiver operating characteristic curves for HBV DNA and HBsAg change from baseline (log) at week 12 showed an area under the curve of 0.521 (p = 0.626) and 0.505 (p = 0.929), respectively (data not shown).

Subgroup analysis

The main baseline demographic and clinical characteristics by subgroup according to treatment pattern (peg-IFNα monotherapy, NUC add-on during peg-IFNα treatment, and NUC add-on during follow-up), ALT level (≤2, >2 and ≤5, and >5 ULN), age (<35 and ≥35 years), treatment duration (48, 72, and 96 weeks), and treatment response (HBV DNA decline >2 log plus ALT increase at week 12 and HBV DNA decline ≤2 log or no ALT increase at week 12) are shown in Table 1. HBV DNA and HBsAg levels were generally similar between subgroups.

The results of the effectiveness end-points by treatment pattern are shown in Table 2. The percentage of patients with HBV DNA <2000 IU/mL at 1 year posttreatment was higher in patients who received NUC add-on (>90%) compared with that in patients who received peg-IFNα monotherapy (79.4%). The percentage of patients with HBsAg loss at EOT, 6 months posttreatment, and 1 year posttreatment who received peg-IFNα monotherapy (6.9%, 10.6%, and 10.6%, respectively) and NUC add-on during peg-IFNα treatment (6.0%, 6.3%, and 7.1%, respectively) was greater as compared with patients who received NUC add-on during follow-up (0, 0, and 0, respectively). In Supplemental Table 3, we summarize the data at EOT, 6 months posttreatment, and 1 year posttreatment by subgroup in patients receiving peg-IFNα monotherapy.

The changes of HBsAg were evaluated by subgroups according to ALT level, age, treatment duration, and treatment

Table 2. Effectiveness end-points by treatment pattern

		EOT	6 months posttreatment	1 year posttreatment
HBV DNA <2000 IU/mL	Peg-IFNα monotherapy	91.8 (88.5, 94.5)	80.6 (75.6, 85.0)	79.4 (73.6, 84.4)
	NUC add-on during peg-IFNα treatment	88.9 (78.4, 95.4)	90.0 (78.2, 96.7)	90.2 (78.6, 96.7)
	NUC add-on during follow-up	63.6 (40.7, 82.8)	78.3 (56.3, 92.5)	94.7 (74.0, 99.9)
HBV DNA <2000 IU/mL and ALT <1 × ULN	Peg-IFNα monotherapy	53.1 (47.6, 58.5)	70.2 (64.4, 75.6)	70.6 (64.1, 76.5)
	NUC add-on during peg-IFNα treatment	41.7 (29.1, 55.1)	77.1 (62.7, 88.0)	83.7 (70.3, 92.7)
	NUC add-on during follow-up	42.9 (21.8, 66.0)	76.2 (52.8, 91.8)	81.3 (54.4, 96.0)
HBsAg loss	Peg-IFNα monotherapy	6.9 (4.5, 10.1)	10.6 (7.2, 14.8)	10.6 (6.9, 15.5)
	NUC add-on during peg-IFNα treatment	6.0 (1.7, 14.6)	6.3 (1.3, 17.2)	7.1 (1.5, 19.5)
	NUC add-on during follow-up	0	0	0
HBsAg seroconversion	Peg-IFNα monotherapy	5.1 (3.0, 8.2)	8.2 (5.2, 12.3)	7.0 (3.9, 11.5)
	NUC add-on during peg-IFNα treatment	7.3 (2.0, 17.6)	5.9 (0.7, 19.7)	9.4 (2.0, 25.0)
	NUC add-on during follow-up	0	0	0

Data are shown as percentage (95% confidence interval).

Abbreviations: ALT, alanine aminotransferase; EOT, end of treatment; FAS-MSC, analysis set of those who meet selection criteria; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NUC, nucleoside analogue; peg-IFNα, pegylated-interferon alpha-2a; ULN, upper limit of normal.

response (Fig. 3). In patients with ALT >5 ULN, HBsAg levels decreased at a slower rate during treatment compared with the subgroups with ALT ≤2 and those with ALT >2 and ≤5 ULN, but a greater decrease in HBsAg level was shown at 1 year post-treatment compared with the other two subgroups. Patients aged <35 years showed a better response in HBsAg decrease over time compared with patients aged >35 years. A marked decrease in HBsAg level was observed in the subgroup receiving treatment for 96 weeks at the EOT compared with those receiving treatment for 48 and 72 weeks, and this tendency remained at 1 year posttreatment. A greater decrease in HBsAg was observed in the subgroup with early response (HBV DNA decline >2 log at week 12 and ALT increase) at EOT and 1 year posttreatment compared with the subgroup with HBV DNA decline ≤2 log at week 12 or no ALT increase at week 12.

The percentages of patients with HBV DNA <2000 IU/mL and HBsAg loss at 1 year posttreatment were not significantly different between subgroups according to baseline ALT level, age, and treatment response at week 12 (data not shown). The percentage of patients with HBV DNA <2000 IU/mL at 1 year posttreatment was 75.6% (95% CI 67.2, 82.8), 84.6% (95% CI 71.9, 93.1), and 89.5% (95% CI 66.9, 98.7), and that of patients with HBsAg loss was 8.5% (4.2, 15.2), 10.0% (3.3, 21.8), and 27.8% (9.7, 53.5) among the subgroups with treatment duration of 48 weeks, 72 weeks, and 96 weeks, respectively.

Safety

The incidence of AEs was 52.0% and that of drug-related AEs was 47.3% (Table 3). Twelve patients (1.3%) had serious AEs. One patient (0.1%) died, but this event was not related to the study drug.

AEs with an incidence ≥10% were decreased white blood (24.7%), platelet (23.4%), and neutrophil counts (21.9%).

Discussion

This is the largest observational study of peg-IFNα therapy in Asian HBeAg-negative CHB patients whose predominant HBV genotypes are B and C. A cut-off of 1 year posttreatment was chosen in the present study because missing HBV laboratory testing data (e.g., HBV DNA and HBsAg, especially quantitative testing data) are unavoidable in observational studies, and the amount of missing data tends to increase with a longer follow-up period. Moreover, the association between 1-year posttreatment response and sustained off-treatment response were reported in a phase 3 study of peg-IFNα.[16]

In the present study, the percentage of patients with HBsAg loss at EOT, 6 months posttreatment, and 1 year posttreatment increased from 6.5% to 9.4% and 9.5%. In an observational study of Korean HBeAg-negative CHB patients who received peg-IFNα therapy for 24 and 48 weeks (the TRACES study),[21] only one patient (1.4%) in the 48-week group presented HBsAg loss at EOT and 6 months posttreatment. In the PegBeLiver study,[22] Caucasian HBeAg-negative patients who received 96 weeks of treatment achieved an HBsAg loss rate of 5.8% compared with 0% in those who received 48 weeks of treatment. Besides the demographic, clinical, and genotype differences between the study populations, the higher HBsAg loss rate at 1 year posttreatment in the present study compared with the TRACES and PegBeLiver studies could have been because our study included patients who received treatment beyond 48 weeks. Our findings were similar to those of another subgroup analysis of Chinese HBeAg-negative patients (the S-COLLATE study),[23] in which the HBsAg loss rate increased from 9% to 12% and 13% at EOT, 6 months post-treatment, and 3 years posttreatment, respectively. In another

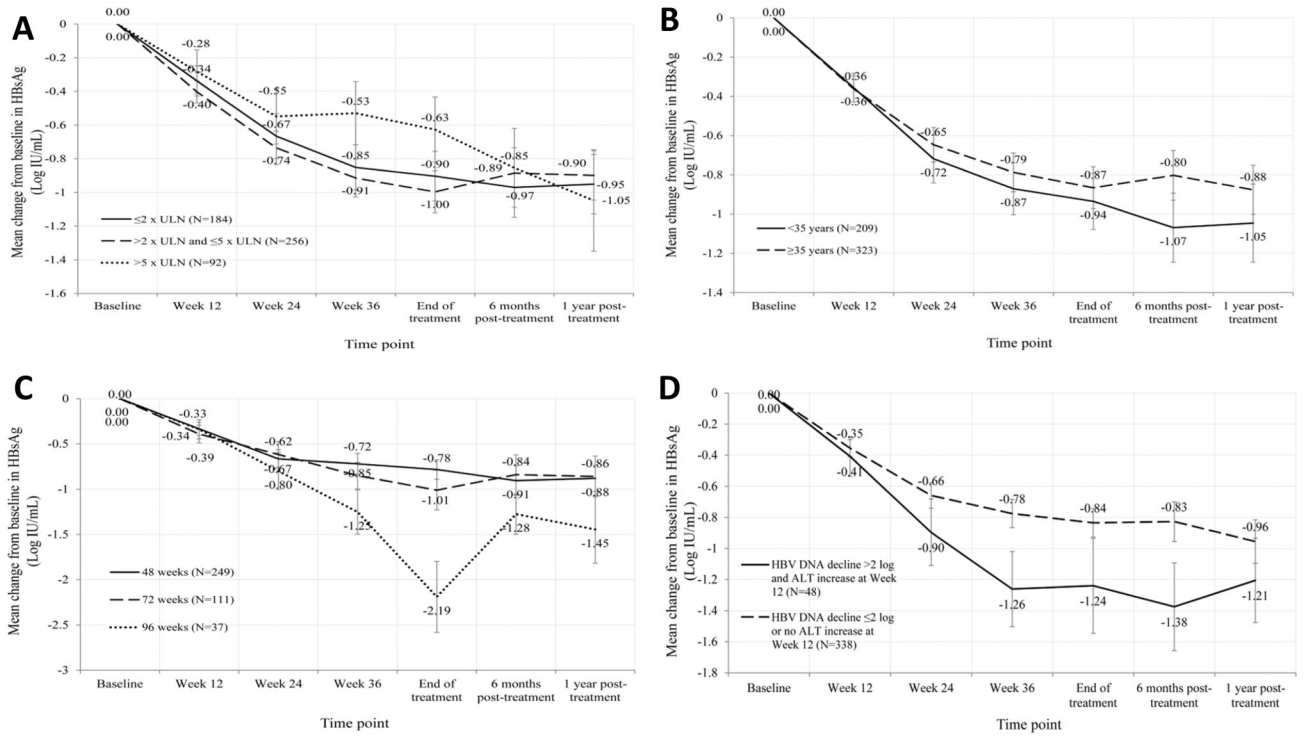

Fig. 3. Changes in HBsAg by subgroup according to ALT (FAS-MSC) (A), age (B), treatment duration (C), and treatment response (D). The error bars indicate standard errors.

Abbreviations: ALT, alanine aminotransferase; FAS-MSC, full analysis set of those who met the selection criteria; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ULN, upper limit of normal.

study of Asian HBeAg-negative patients,[17] HBsAg loss at 48 weeks posttreatment was 10.5% in patients who received 48 weeks of treatment (which was similar to the HBsAg loss rate at 1 year posttreatment in the present study, 10%) and 33.3% in those who received 72 weeks of treatment.

The Chinese consensus on peg-IFNα in treatment of CHB published recently emphasizes that for patients with suboptimal response (i.e. HBsAg decline >1 log at week 24, but not achieving HBsAg loss at week 48), extended treatment duration to 72 or 96 weeks helps patients achieve functional cure.[24] The present study showed a marked HBsAg level decrease from 24 weeks to 96 weeks in patients who received 96 weeks of treatment compared with those who received 48 weeks of treatment, and provides further evidence for the extended treatment duration preferred by medical practitioners in China.

Table 3. Adverse events

Adverse event	Total, *n* = 930
Any	484 (52.0%)
Any drug-related	440 (47.3%)
Any SAE	12 (1.3%)
Any drug-related SAE	4 (0.4%)
Any leading to discontinuation from treatment	81 (8.7%)
Any leading to dose adjustment	114 (12.3%)
Any leading to death	1 (0.1%)
Any drug-related leading to death	0
White blood cell count decreased	230 (24.7%)
Platelet count decreased	218 (23.4%)
Neutrophil count decreased	204 (21.9%)

Data are shown as *n* (%).
Abbreviation: SAE, serious adverse event.

In the present study, the percentage of patients with HBV DNA <2000 IU/mL was 90.0% at EOT, 81.8% at 6 months posttreatment, and 82.2% at 1 year posttreatment. In the TRACES study,[21] the percentage of patients with HBV DNA <2000 IU/mL was 87.8% at EOT and 47.3% at 6 months posttreatment. In a study of Asian HBeAg-negative patients,[17] the HBV DNA suppression rate at 48 weeks post-treatment was 60.5% in patients who received 48 weeks of treatment and 83.3% in those who received 72 weeks of treatment. The longer treatment duration in the present study may have contributed to the higher HBV DNA suppression rate at 6 months and 1 year posttreatment in our study versus previous studies. However, undocumented NUC add-on treatment is suspected (e.g., patients may have self-prescribed NUC add-on or it may have been prescribed by other health care providers when patients sought medical attention in other hospitals). Unlike HBsAg, NUC add-on treatment has a significant effect on HBV DNA suppression, and thus, NUC add-on treatment may have confounded the results.

Regarding predictors of response, in HBeAg-negative CHB patients with genotype D, a combination of no decrease in HBsAg levels and <2 log IU/mL reduction in serum HBV DNA

levels at 12 weeks of Peg-IFNα therapy is associated with no response to treatment, and these characteristics should be considered as criteria for peg-IFNα treatment discontinuation.[11] However, no robust treatment discontinuation criteria have been developed for HBeAg-negative CHB patients with genotype B or C.[11] Based on clinical experience, Chinese clinical experts recommend peg-IFNα treatment discontinuation at week 24 if HBsAg decreases to <1 log IU/mL and HBV DNA decreases to <2 log IU/mL.[24] Unfortunately, no statistically significant relationship was found between baseline factors and HBV DNA suppression at 1 year posttreatment in the present study, and no evidence was generated to support treatment discontinuation at week 12 or week 24 for HBeAg-negative patients dominated by genotype B or C.

Regarding the changes in HBsAg by subgroups, in patients with ALT >5 ULN, HBsAg levels decreased at a slower rate during treatment compared with the subgroups with ALT ≤2 and those with ALT >2 and ≤5 ULN, but a greater decrease in HBsAg level was shown at 1 year posttreatment in patients with ALT >5 ULN compared with the other two subgroups. Reportedly, in patients with CHB, an ALT level ≥200 IU/L is associated with HBsAg seroclearance.[14,25,26] Such increased levels of ALT indicate that HBV-infected hepatocytes have triggered a strong host immune response which is likely a result of the immunomodulating effects of peg-IFN[27] that will eventually lead to anti-HBe seroconversion and HBV DNA reduction. Thus, it is easier for patients with high ALT to achieve HBsAg clearance. Additionally, the effect of ALT seemed to be more obvious after discontinuation, which may be related to the mobilization of the immunity.

Among the 930 patients in the FAS who were evaluated for safety in the present study, more than half presented AEs and the most common AEs were decreased white blood, platelet, and neutrophil counts. These findings were similar to the peg-IFNα safety profile identified in peg-IFNα labeling.[28].

The present study has some limitations, including those inherent to observational studies and inadequately controlled confounders. Although the study was designed to document potential confounders and adjustments for these potential confounders were made in the statistical analysis, residual confounding may still exist. In clinical practice, patients cannot attend visits at predefined times as in interventional studies. If we had considered patients with missing data as nonresponders, this would have resulted in a considerable underestimation of treatment outcomes. Thus, analyzing patients with available data is more reasonable in this situation.

In conclusion, peg-IFNα showed good effectiveness and was well tolerated by HBeAg-negative CHB Chinese patients in routine clinical practice in China. Additionally, our results suggest that a certain proportion of HBeAg-negative patients have the potential to achieve functional cure (HBsAg loss) with the use of peg-IFNα; however, 48 weeks of treatment may not be sufficient.

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Conflict of interest

Qianguo Mao has received grants and Jidong Jia has received grants and personal fees from Shanghai Roche Pharmaceuticals Ltd. during the conduct of this study. Yan Huang is an employee of Shanghai Roche Pharmaceuticals Ltd. The other authors have no conflict of interests related to this publication.

Author contributions

Contributed to the design of the study and/or collection and analysis of the data, drafting/critical revision of the manuscript for intellectual content, played a role in final approval for publication of the manuscript, and agrees to be accountable for the accuracy and integrity of the published work (YH), and contributed to the design of the study and/or collection and analysis of the data, played a role in final approval for publication of the manuscript, and agree to be accountable for the accuracy and integrity of the published work (XC, QM, YX, XD, QX, JS, ZG, XZ, YL, HZ, SZ, SL, FZ, YX, MZ, YH, XC, HR, and JJ).

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