Annals of Hepatology

The Official Journal of the Mexican Association of Hepatology, the Latin-American Association for Study of the Liver and the Canadian Association for the Study of the Liver

ORIGINAL ARTICLE

Clinical Analysis of Polyethylene Glycol Interferon-α Treatment in 155 Hepatitis B e Antigen (HBeAg)-Positive Chronic Hepatitis B (CHB) Patients

Xin Luo, Ji-Xian Yu, Lei Xie, Wen-Jun Ma, Li-Hong Wang

Department of Hepatology, Xixi Hospital of Hangzhou, Hangzhou, China.

ABSTRACT

Purpose. This study aims to investigate the antiviral effect of polyethylene glycol (PEG)-interferon α-2a and PEG-interferon α-2b treatment on hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB) at the 48th week of treatment and the 24th and 48th week after withdrawal, in order to provide guidance on the antiviral treatment of HBeAg-positive CHB patients. **Material and methods.** Antiviral treatment was performed on 155 HBeAg-positive CHB patients. Among these patients, 66 patients received PEG-interferon α-2a treatment and 89 patients received PEG-interferon α-2b treatment; and these treatments were administered by subcutaneous injection, once per week, which lasted for 48 weeks. Other antiviral and hepatoprotective drugs were not used during the treatment. **Results.** At the 48th week of treatment, ALT recovery rate, HBsAg seroconversion rate, HBeAg seroconversion rate and HBV DNA titers dropped below 200 IU/mL rate were 69.7%, 6.1%, 27.3% and 50.0%, respectively, in the PEG-interferon α-2a group; and were 70.8%, 6.7%, 33.7% and 62.9%, respectively, in the PEG-interferon α-2b group. At the 24th and 48th week of follow-up after withdrawal, HBsAg seroconversion rate in these two groups did not change; and HBeAg seroconversion rate further increased. Furthermore, HBV DNA revealed a low recurrence rate. The difference between these two groups was not significantly significant. **Conclusions.** PEG-interferon α-2a and PEG-interferon α-2b are effective antiviral drugs for the treatment of HBeAg-positive CHB, which has a HBsAg seroconversion rate of more than 5%. Furthermore, this sustained response effect was maintained at the 24th and 48th week of follow-up after withdrawal.

Key words. CHB. Antiviral effect. PEG interferon-α.

INTRODUCTION

CHB remains a global public health problem,[1-3] and China currently has the largest number of individuals infected with hepatitis B virus (HBV) in the world. Clinical reports[4] have revealed that CHB patients do not generally manifest any specific symptom. However, the incidence of liver cirrhosis and liver cancer remains high, and is considered a serious threat to the life and health of patients. At present, there is currently no existing drug that can thoroughly cure hepatitis B.[5-7] As pointed out by the 2010 Guidelines for the Prevention and Treatment of CHB,[8] if CHB patients in the active phase show indications, standard anti-HBV treatment should be performed. This treatment includes interferon and nucleoside drugs. Furthermore, based on the guidelines of the American Association for the Study of Liver Diseases (AASLD), PEG-interferon α is recommended as the first-choice drug when taking into account the long-term nature of antiviral therapy and the risk of drug-resistance in long-term treatment.[9] In this study, we retrospectively investigated the antiviral effect of PEG-interferon α-2a and PEG-interferon α-2b for treating HBeAg-positive CHB, in order to provide guidance on antiviral treatment for HBeAg positive CHB patients.

Manuscript received: December 08, 2016. **Manuscript accepted:** April 18, 2017.

DOI:10.5604/01.3001.0010.5279

MATERIALS AND METHODS

Study subjects

A total of 155 HBeAg-positive CHB patients in the outpatient or inpatient of our hospital from January 2011 to June 2012 were enrolled according to the following criteria:

- **Antiviral treatment:** Positive HBeAg patients, HBV DNA ≥ 20,000IU/mL; ALT Continuous Elevation ≥ 2×ULN (more than 3 months) and ≤ 10 x ULN, serum total bilirubin < 2 x ULN.
- Patients who never used anti-HBV drugs.
- **Age:** 8-50 years old.
- Patients who are willing to use peg-IFN α-2a or PEG-interferon α-2b and signed informed content.

Meanwhile, the following conditions were excluded:

- Patients who have absolute or relative contraindications for interferon.
- Patients who suffered liver cirrhosis and other serious organ diseases.
- Patients who can not bear adverse reaction of interferon. Among these patients, 66 patients received PEG-interferon α-2a treatment.

Among these 66 patients, 52 patients were male and 14 patients were female; and the age of these patients ranged between 17-48 years old, with an average age of 29.61 ± 7.91 years old. These patients were given a dose of 135 μg/week. The remaining 89 patients received PEG-interferon α-2b treatment. Among these patients, 69 patients were male and 20 patients were female; nd the age of these patients ranged between 9-43 years old, with an average age of 26.67 ± 7.06 years old. These patients were given a dose of 1-1.5 μg/kg/week. All treatment protocols were administered through subcutaneous injection, which lasted for 48 weeks. Other antiviral and hepatoprotective drugs were not used during the treatment. These selected patients met the interferon therapy indications written in the Guidelines for the Prevention and Treatment of CHB, and were diagnosed with HBeAg-positive CHB.

Detection index

During treatment, the following items were regularly monitored: blood routine, liver ("ALT recovery" means that ALT comes to the normal level, < 50U/L) and kidney function, myocardial enzyme spectrum, electrolyte, serum HBV markers, HBV DNA ("HBV DNA titers dropped below 200 IU/mL" means that HBV DNA comes to the negative, < 200 IU/mL), and thyroid function. Serum HBV markers in all patients were quantitatively determined by electrochemiluminescence using the Architect i2000 Immunoassay Analyzer (Abbott Laboratories, USA), HBsAg was tested with chemiluminescence. Serum DNA HBV quantitation was conducted using a PE5700 PCR amplification instrument (a result < 200 IU/mL was determined as negative).

Statistical methods

Data was analyzed using statistical software SPSS 11.5. Measurement data were expressed as mean ± standard deviation (x ± SD). χ^2 test was used to compare count data between these two groups, comparison of age, ALT and HBV-DNA by t test, and $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of baseline situations between these two groups of patients

Baseline situations of patients in the PEG-interferon α-2a and PEG-interferon α-2b groups: Differences in male-to-female ratio, average age, baseline ALT levels and baseline DNA HBV levels between these two groups was not statistically significant ($P > 0.05$). These results are shown in table 1.

Response in patients in these two groups at the 48th week of treatment

At the 48th week of treatment, ALT recovery rate, HBsAg seroconversion rate, HBeAg seroconversion rate and HBV DNA titers dropped below 200 IU/mL rate were 69.7%, 6.1%, 27.3% and 50.0%, respectively, in the PEG-interferon α-2a group; and were 70.8%, 6.7%, 33.7% and 62.9%, respectively, in the PEG-interferon α-2b group. Overall response rate was higher in the PEG-interferon α-2b group than in the PEG-interferon α-2a group. However, the difference between these two groups was not significantly significant ($P > 0.05$). These results are shown in table 2.

Response situations in patients in these two groups at the 48th week after drug withdrawal

At the 48th week of treatment, ALT recovery rate, HBsAg seroconversion rate, HBeAg seroconversion rate

Table 1. Comparison of baseline in two groups.

Baseline	PEG-interferon α-2a treatment group	PEG-interferon α-2b treatment group	P value
M/F	3.71:1 (52:14)	3.45:1(69:20)	> 0.05
Average age	29.61 ± 7.91	26.67 ± 7.06	>0.05
Baseline ALT levels(U/L)	292.73 ± 254.78	267 ± 303.68	>0.05
Baseline DNA HBV levels (logIUIU/mL)	7.09 ± 0.44	6.92 ± 0.47	>0.05

Table 2. Response in patients in these two groups at the 48th week of treatment.

	PEG-interferon α-2a treatment group	PEG-interferon α-2b treatment group	P value
ALT recovery, number(%)	46 cases (69.7%)	63 cases (70.8%)	>0.05
HBsAg seroconversion, number(%)	4 cases (6.1%)	6 cases (6.7%)	>0.05
HBeAg seroconversion, number(%)	18 cases (27.3%)	30 cases (33.7%)	>0.05
HBV DNA titers dropped below 200 IU/mL, number(%)	33 cases (50.0%)	56 cases (62.9%)	>0.05

Table 3. Response situations in patients in these two groups at the 48th week after drug withdrawal.

	PEG-interferon α-2a treatment group	PEG-interferon α-2b treatment group	P value
ALT recovery, number(%)	49 cases (74.2%)	67 cases (75.2%)	> 0.05
HBsAg seroconversion, number(%)	4 cases (6.1%)	6 cases (6.7%)	> 0.05
HBeAg seroconversion, number(%)	23 cases (34.8%)	33 cases (37.1%)	> 0.05
HBV DNA titers dropped below 200 IU/mL, number(%)	35 cases (53.0%)	56 cases (62.9%)	> 0.05

and HBV DNA titers dropped below 200 IU/mL rate were 74.2%, 6.1%, 34.8% and 53.0%, respectively, in the PEG-interferon α-2a group; and were 75.2%, 6.7%, 37.1% and 62.9%, respectively, in the PEG-interferon α-2b group. This response effect was maintained in these two groups of patients at the 48th week after withdrawal. These results are shown in table 3.

DISCUSSION

HBV infection-related liver failure, cirrhosis and primary liver cancer are a serious threat to the life of patients. The anti-HBV mechanism of interferon-α includes direct antiviral effect and immunoregulation.[10-12] Interferon-a can inhibit viral DNA replication, degrade viral RNA, inhibit the synthesis and transport of viral protein, and block the secretion of mature virus. In addition, its immunological mechanism is more complicated. PEG-interferon a derives from interferon-α through the addition of a large volume of branched PEG molecules, which increases the molecular weight of interferon and reduces drug excretion, shields the antigenic determinant on the surface of interferon molecules, and reduces immunogenicity and the clearance rate of interferon in the body. Furthermore, it slows down the hydrolysis of protease, in which its half-life can be prolonged up to 40 h. This enables interferon to continuously work in the body, and effectively improves the antiviral effect.[13] In addition, PEG-interferon is mainly metabolized in the liver. Hence, it can selectively exert on the target organs of hepatitis, playing the dual role of immunoregulation and antiviral action. It was reported by Zhe Li[14] that in PEG-interferon treatment for hepatitis B, HBeAg seroconversion rate could reach 48%, HBV DNA titers dropped below 200 IU/mL rate was more than 50%, ALT and AST recovery rate was up to 35%, histological improvement rate was 67%, and 9% of the patients underwent HBsAg-negative conversion. Through studies, some Chinese scholars considered that the clinical effect of long-term interferon was better than that of conventional interferon.[15-17] Phase II clinical trials have revealed that PEG-interferon α-2a is superior to conventional interferon in the treatment of HBeAg-positive CHB.[18] The study of Chan, *et al*. demonstrated[19] that HBsAg in 5% (2/40) of CHB patients became negative after PEG-interferon α-2a treatment. Pisit, *et al*.[20] reported that 48 weeks after PEG-interferon α-2b treatment, 33.3% HBeAg-positive CHB patients underwent HBeAg seroconversion and HBV DNA negative conversion. However, there is cur-

rently no large-sample controlled study in China. In this study, 66 patients received PEG-interferon α-2a treatment and 89 patients received PEG-interferon α-2b treatment. Differences in male-to-female ratio, average age, baseline ALT levels and baseline DNA HBV levels between these two groups were not statistically significant ($P > 0.05$). At the 48th week of treatment, ALT recovery rate, HBsAg seroconversion rate, HBeAg seroconversion rate and HBV DNA titers dropped below 200 IU/mL rate were 69.7%, 6.1%, 27.3% and 50.0%, respectively, in PEG-interferon α-2a group; and were 70.8%, 6.7%, 33.7% and 62.9%, respectively, in the PEG-interferon α-2b group. These results demonstrated that at the 48th week of treatment for HBeAg-positive CHB, both PEG-interferon α-2a and PEG-interferon α-2b revealed a higher antiviral response. HBsAg seroconversion rates were all over 5%. Overall response rate was higher in the PEG-interferon α-2b group than in the PEG-interferon α-2a group, but the difference between these two groups was not significantly significant ($P > 0.05$). An international multicenter randomized controlled clinical trial has revealed that in HBeAg-positive CHB patients who received 48 weeks of PEG-interferon treatment, HBeAg serum conversion rate was 43% at the 48th week follow-up after withdrawal. Results of this study revealed that in these two groups of patients, at the 48th week follow-up, HBsAg seroconversion rates did not change, HBeAg seroconversion rate further increased, and HBV DNA exhibited a low recurrence rate; suggesting that the response effect of PEG-interferon α was sustained after withdrawal, and difference between the two groups was not significantly significant.

Through this study, PEG-interferon α-2a and PEG-interferon α-2b were found to be effective for treating HBeAg-positive CHB, with a HBsAg seroconversion rate of more than 5%, and a sustained response effect at the 48th week follow-ups after withdrawal. HBeAg positive CHB patients, who have conditions, should give priority to PEG-interferon a treatment.

CONFLICT OF INTEREST

None.

REFERENCES

1. Lok AS, McMahon BJ. Chronic hepatitis B: update of recommendations. *Hepatology* 2004; 39(3): 857-61.
2. Lai CL, Ratziu V, Yuen MF, Thierry P. Viral hepatitis B. *Lancet* 2003; 362(9401): 2089-94
3. Chen Y, Chen YP, Tao RF. The research progress of chronic hepatitis B. *China Medicine* 2011; 6(4): 500-2.
4. Ren X, Xu Z, Liu Y, Li X, Bai S, Ding N, Zhong Y, et al. Hepatitis B virus genotype and basal core promoter/precore mutations are associated with hepatitis B-related acute-on-chronic liver failure without pre-existing liver cirrhosis. *J Viral Hepatology* 2010; 17(12): 887-95.
5. Jiang ZW and Liu X. The study of the consequence about α-interferon and Hepatitis B virus genotype of B and C on the treatment of chronic Hepatitis B. *Modern Medicine* 2013; 41(3): 205-7.
6. Zhang WW, Han ZY. The study of the consequence about acupoint injection α-interferon on the treatment of chronic Hepatitis B. China's health care nutrition 2012; 2(7): 1767-8.
7. Li WL, Wu MS, Huang YB. The expression of peripheral blood mononuclear cells TLR4 and the change of serum type Th1/Th2 cytokines on the α-interferon treatment of chronic Hepatitis B. *Practical Hepatology* 2012; 15(4): 315-17.
8. Chinese Society of Hepatology and Chinese Society of Infectious Diseases: The guideline of prevention and treatment of chronic hepatitis B (2010). *Chin J Hepatol* 2011; 19(1): 13-24.
9. Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000-summary of a workshop. *Gastroenterology* 2001; 120: 1828-53.
10. Li HQ, Li H. The antiviral mechanism and effect of interferon on viral hepatitis. *China Public Health* 2005; 22(7): 890-91.
11. Xu BF, Fan QL, Wei W, Song LH. The advance of the anti-hepatitis virus mechanisms about α-interferon and peg-interferon. *Chinese Pharmacological Bulletin* 2008; 14(10): 1276-9.
12. Lin Q, Yu XP, Su ZJ. The curative effect analysis of partial response of nucleoside analogues on the treatment of chronic hepatitis B to continue with the alpha interferon. *Practical Hepatology* 2013; 16(3): 232-4.
13. You CY. Analysis of the adverse drug reactions of α-interferon on the treatment of chronic hepatitis B. *Clinical rational Drug Use* 2013; 6(2): 53.
14. Li Z. The clinical observation of Peg-interferon α-2 a180 μg combined with adefovir on the treatment of chronic hepatitis B. *The latest medical information abstract* 2012; 12(10): 267-268.
15. Shi YY. The clinical observation of peg-interferon compared with conventional interferon on treatment of 60 cases of chronic hepatitis B. *Public Medical Forum* 2015; 19(5): 640-2.
16. Wang Y, Liu SM. The research of the side effects and clinical significance of alpha interferon on the treatment of chronic hepatitis B. *Chin J Biochem Pharm* 2014, 7(34): 126-8.
17. Chen YF, Zhang W, Qiu LL. The effect comparison of Peg-interferon with conventional interferon on treatment of chronic hepatitis B. *Clinical Medical* 2013; 22(7): 94-5.
18. Cooksley WG, Piratvisuth T, Lee SD, Mahachai V, Chao YC, Tanwandee T, Chutaputti A, et al. Peginterferon α-2a(40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. *J Viral Hepatitis* 2003; 10: 298-305.
19. Chan HL, Wong VW, Chim AM, Lai HC, Huang CF, Hsieh MY, Huang JF, et al. Treatment of patients with chronic hepatitis B who have failed previous antiviral treatment with pegylated interferon alpha-2a. *Antiviral therapy* 2008; 13: 555-62.
20. Tangkijvanich P, Komolmit P, Mahachai V, Sa-Nguanmoo P, Theamboonlers A, Poovorawan Y. Comparison between quantitative hepatitis B surface antigen, hepatitis B e-antigen and hepatitis B virus DNA levels for predicting virological response to pegylated interferon α-2b therapy in hepatitis B e-antigen-positive chronic hepatitis B. *Hepatology Research* 2010; 40: 269-77.

Correspondence and reprint request:
Ji-Xian Yu, M.D.
Department of Hepatology
Xixi Hospital of Hangzhou.
Hengbu Street 2, Xihu District, Hangzhou, 310023, China
Tel: +86 571 8648 1692. Fax: +86 571 8648 1700
E-mail: jixianyudoc@163.com