Original Article

Comparing Standard Interferon and Interferon Conjugated with Polyethylene Glycol for Treatment of Patients Chronically Infected with Hepatitis B Virus Infection

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Abstract

Background: The efficacy of interferon (IFN) has recently improved by the replacement of standard IFN by the type conjugated with polyethylene glycol IFN (PEG IFN). However, the superiority of PEG IFN regimen to therapy with standard IFN remains uncertain. **Objectives:** The present study aimed to assess and compare the efficacy of the two standard IFN and PEG IFN regimens for the treatment of patients chronically infected with hepatitis B virus (HBV) infection. **Materials and Methods:** The present study was conducted as a retrospective, cohort study assessing 138 consecutive patients diagnosed as a case infected chronically with HBV. The patients were randomly assigned to receive standard IFN regimen ($n = 71$) intravenously or PEG IFN regimen ($n = 67$) intravenously for total 24 weeks. All patients were monitored monthly regarding serum aminotransferase level and hepatitis B e antigen (HBe-Ag) positivity as the viral load. **Results:** Overall, 8.4% in standard IFN group and 10.4% in PEG IFN responded to the treatment regimens with no between-group difference ($P = 0.715$). The response to treatment protocols was independent to gender, age, and viral load. In addition, 66.7% responded to standard IFN regimen, and 42.9% responded to PEG IFN regimen were positive for HBe-Ag with no difference between the two protocols ($P = 0.639$). Adjusted for HBe-Ag positivity, the type of IFN used for the treatment of chronic hepatitis B infection could not be effective factor (odds ratio = 0.792, $P = 0.690$). **Conclusion:** Our study could not demonstrate the superiority of PEG IFN to standard IFN for treating chronic HBV infection.

Keywords: Chronically infected with hepatitis B, infection, interferon, polyethylene glycol treatment

Introduction

Epidemiologically, about 350 million people infected with hepatitis B virus (HBV) entire the world leading up to 600,000 deaths annually due to life-threatening complications of infection including liver failure and fulminant hepatitis, encephalopathy, liver cirrhosis, and hepatocellular carcinoma.[1,2] In a notable number of affected patients, the feature of disease may change to chronic condition, so about 1.5 million persons are chronically infected with hepatitis B only in the United States.[3,4] Fortunately, by developing proper vaccination, the incidence of new hepatitis B infection has been globally declined.[5] The main goal of treatment for hepatitis B infection, especially in chronic condition is to reduce the risk for liver inflammation and thus destruction through inhibiting virus replication in liver tissue.[6] In this regard, some therapeutic options have been developed to achieve this goal including medications that are prescribed intravenously, orally, or even subcutaneously.[7,8] In parallel with drug treatment, the patients undertreated should be continuously monitored for disease activity through checking liver functional enzymes or even diagnostic liver biopsy.

The common and standard treatment option that is globally used for many years includes interferon (IFN) alfa. This drug can induce its antiviral effect via to mechanisms including inhibition of viral DNA synthesis through activating some antiviral enzymes and also increasing cellular immune response against hepatocytes infected with virus by stimulating immune cells such as T helper and natural killer lymphocytes.[9] The efficacy of various regiments of this medication could demonstrate its high efficacy regarding loss

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of hepatitis B antigens.[10] However, some contradictory results have been achieved with respect to treatment response rate due to employing different drug regimens as well as to different level of drug tolerability.[11-13]

Recently, the efficacy of IFN has improved by the replacement of standard IFN by IFN conjugated with polyethylene glycol IFN (PEG IFN). This change aimed to reduce excretion of IFN by the kidneys leading an increase in IFN half-life and thus increase in its plasma stability. Some randomized trials have shown that the PEG IFN regimen could be twice as effective as the corresponding standard IFN regimen with comparability in drugs-related safety and side effects.[14-16] However, the superiority of PEG IFN regimen could not be proven in some other trials needing an implementation of further comparative studies. The present study aimed to assess and compare the efficacy of the two standard IFN and PEG IFN regimens for the treatment of patients chronically infected with HBV infection.

Materials And Methods

The present study was conducted as a retrospective cohort study assessing all consecutive patients diagnosed as a case infected chronically with HBV that referred to hepatitis clinic at Imam Khomeini hospital in Tehran, Iran, during 2015 and 2016. All patients with positive serum HBs-Ag for at least 6 months with one of the following criteria were considered to be eligible for the study: (1) the patients older than 30 years with serum HBV-DNA higher than 2000 units and an abnormal aminotransferase (ALT) level (≥30 IU/L for men and ≥19 IU/L for women) in two consecutive tests within 6 months; (2) the patients younger than 30 years with serum HBV-DNA higher than 2000units and an abnormal ALT level (≥30 IU/L for men and ≥19 IU/L for women) in two consecutive tests within 6 months if evidence of fibrosis was found in liver biopsy or with fibroelastography score more than 6 kpu; (3) all subjects with virus level higher than 20,000 or suffering reversible cirrhosis with measurable level of virus. The following were also considered as the exclusion criteria: HIV or HDV co-infection, pregnancy, drug abuse, or irreversible cirrhosis. At the beginning of treatment planning, the levels of liver enzymes and hepatitis B e antigen (HBe-Ag) were quantitatively measured, and the viral load was also determined using the PCR technique. The severity of liver lesions was also assessed by biopsy or by fibroelastography. The patients were randomly assigned to receive standard IFN regimen (daily) intravenously or PEG IFN regimen (weekly) intravenously for total 24 weeks. All patients were monitored monthly regarding serum ALT level and drug-related side effects. At the end of 24 weeks, HBV-Ag positivity as the viral load was reassessed. The treatment protocol was considered unresponsive and discontinued if the level of virus reduced less than $2\log_{10}$ IU/ml or the level of HBe-Ag reached to higher than 20,000.

Results were presented as mean ± standard deviation for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov–Smirnov test. Categorical variables were compared using Chi-square test or Fisher's exact test when more than 20% of cells with expected count of >5 were observed. Quantitative variables were also compared with *t*-test or Mann-Whitney U test. For the statistical analysis, the statistical software SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used. $P \leq 0.05$ was considered statistically significant.

The study was conducted according to the Declaration of Helsinki and participants signed an informed consent form approved by the Ethics Committee of the Faculty of Medicine (Code: 94163).

Results

A total of 138 patients (91 men and 47 women) referred to our clinic with chronic hepatitis B infection that 71 were treated with standard IFN regimen and 67 with PEG IFN regimen. The two groups were comparable in gender distribution, mean age, positive HBe-Ag test, and mean viral load [Table 1]. Overall, 6 out of 71 patients (8.4%) in standard IFN group and 7 out of 67 patients (10.4%) in PEG IFN responded to the treatment regimens with no between-group difference ($P = 0.715$). Regarding response to treatment protocols in terms of patients' characteristics, in men, the positive response to standard IFN regimen was 11.6% while this response rate to PEG IFN regimen was shown to be 10.4% with no significant difference ($P = 0.869$). In women, the treatment response to standard IFN and PEG IFN regimens was 3.6% and 10.5%, respectively with no difference ($P = 0.565$). The mean age of patients responded to standard IFN regimen, and PEG IFN regimen was 35.83 ± 14.13 years and 36.14 ± 10.94 years indicating no significant difference across the two groups ($P = 0.336$). In each group of regimens, no difference was found in mean age between the responded and nonresponded ones [Table 2]. In addition, 4 of 6 patients (66.7%) responded to standard IFN regimen, and 3 of 7 patients (42.9%) responded to PEG IFN regimen were positive for HBe-Ag with no difference between the two protocols ($P = 0.639$). As shown in Table 3, the type of IFN used for treatment of chronic hepatitis B infection could not be effective factor adjusted for viral load (odds ratio = 0.792, $P = 0.690$).

Discussion

The main goal of treating chronic HBV infection is to prevent liver inflammatory damages through virus inactivation through virus genomic suppression leading inhibition of virus replication. This approach can effectively reduce the risk for both inflammatory and carcinogenic liver disorders. The standard indices of liver normalization following treatment include normalization of serum liver enzymes, especially ALT, HBe-Ag negativity, decreasing the circulatory level of virus DNA, and evidence of the improvement of liver

Table 1: Baseline characteristics in the two groups receiving different interferon regimens

	Standard IFN group (n=71)	PEG IFN group (n=67)	P
Gender			
Men	43 (60.6)	48 (71.6)	0.534
Women	28 (39.4)	19 (28.4)	
Age (year)	35.95±12.93	36.20±10.22	0.226
Positive HBe-Ag	38 (53.5)	35 (52.2)	0.933
Viral load	63,848,730.69±172,867,978.70	61,000,094.72±222,963,232.90	0.964

IFN: Interferon, PEG IFN: Polyethylene glycol interferon, HBe-Ag: Hepatitis B e-antigen

Table 2: Response to treatment in two interferon regimens according to baseline variables

	Standard IFN group (n=71)	PEG IFN group (n=67)	P
Male			
Responded	5 (11.6)	5 (10.4)	0.869
Nonresponded	38 (88.4)	43 (89.6)	
Female			
Responded	1 (3.6)	2 (10.5)	0.565
Nonresponded	27 (96.4)	17 (89.5)	
Mean age, year			
Responded	35.83±14.13	36.14±10.94	0.336
Nonresponded	36.06±11.72	36.25±9.50	
Positive HBe-Ag			
Responded	4/6 (66.7)	3/7 (42.9)	0.639
Nonresponded	34/65 (52.3)	32/60 (53.3)	

IFN: Interferon, PEG IFN: Polyethylene glycol interferon, HBe-Ag: Hepatitis B e-antigen

Table 3: Difference in response to interferon regimens adjusted for viral load

Item	Beta	SE	Wald	P	OR
Type of IFN	−0.234	0.585	0.160	0.690	0.792
Viral load	0.000	0.000	0.001	0.975	1.000
Constant	−1.918	0.912	4.419	0.036	0.147

OR: Odds ratio, SE: Standard error, IFN: Interferon

tissue histology.[5,6] Several medications have been used to treat chronic HBV infection. Some recent studies comparing both common regimens including standard IFN and PEG IFN could show higher effectiveness of PEG IFN, with a similar adverse effect profile. However, some other trials such as our experience did not demonstrate the superiority of PEG IFN compared to standard IFN. This discrepancy might be due to several factors such as factors related to study design (observational or interventional nature), different drug regimens regarding dosages and duration of treatment, and considering different time points for assessing treatment outcome. PEG IFN is now accepted as a well-tolerated drug in well-compensated patients with the common order of once weekly from 6 to 12 months. Some studies could show that using treatment protocol including PEG IFN, half of the patients with HBeAg-positive genotype a infections will achieve seroconversion.[1] However, this change may not be revealed up to 6 months after therapy[6] that may be a good explanation on our observation that the change in viral load following treatment was observed in few patients treated. However, similar to most antiviral medications, administration of PEG IFN may be accompanied with some adverse side effects. First, the use of this drug must not be considered in patients with advanced liver disease or in those co-infected with HIV, and thus it may be remained unless in most patients. Moreover, long-term use of this drug may result in some potential complication, and thus beneficial advantages of long-term prescription of PEG IFN remains unknown.

HBsAg quantification is effective in guiding the therapy of PEG-IFN in patients with chronic hepatitis B. In this regard; it seems that the time point considered for assessing this biomarker is very important to assess the effectiveness of PEG-IFN regimen. As shown recently in a meta-analysis,[17] at week 12 of beginning the treatment by this drug, the patients without optimal on-treatment HBsAg levels have hardly achieved a response with the early nonresponse rate of 99%, while 12 weeks later, the response rate increase to 79% in HBeAg-negative patients. Some others[18] could show that baseline HBeAg level in combination with HBV DNA may become an effective predictor for guiding optimal therapy with PEG-IFN against HBe-Ag-positive chronic hepatitis B. In our study, we only check HBe-Ag for assessment of viral load at a single time point at the end of 24 weeks of completing the treatment. It seems that using a combination of monitoring biomarkers, especially genome-based markers such as DNA of virus can be more helpful to monitor optimal therapy with PEG IFN.

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Conflicts of interest

There are no conflicts of interest.

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