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An Observational, Multicenter, Cohort Study Evaluating the Antiviral Efficacy and Safety in Korean Patients With Chronic Hepatitis B Receiving Pegylated Interferon-alpha 2a (Pegasys)

TRACES Study

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Abstract: Currently, limited data are available regarding the efficacy and safety of pegylated interferon alpha-2a (PEG-IFN α -2a) in Korean patients with chronic hepatitis B (CHB), in whom hepatitis B virus (HBV) genotype C is the most common type.

We collected data from 439 patients (HBeAg positive, $n = 349$; HBeAg negative, $n = 90$) with CHB who were treated with PEG-IFN α -2a as a first-line therapy from 18 institutions. Treatment responses at the end of treatment (ET) and at 6 months posttreatment (PT6) were compared between the patients who were treated for 24 weeks versus 48 weeks, and adverse events (AEs) were evaluated.

In HBeAg-positive patients, those who received PEG-IFN α -2a for 48 weeks showed significantly higher HBV DNA suppression (HBV DNA < 2000 IU/mL) than those who were treated for 24 weeks (48

weeks vs 24 weeks; at ET, 44.4% vs 36.7%, $P = 0.035$; at PT6, 35.9% vs 13.3%, $P = 0.035$). The HBeAg seroconversion rate at ET was 18.1% in 48-week treatment group, which is significantly higher than the 2.2% ($P < 0.001$) that was seen in 24-week treatment group. This finding also continued at PT6 (29.0% vs 10.0%, $P < 0.001$). Following 48 weeks of treatment in HBeAg-negative patients, HBV DNA suppression at ET was higher than in HBeAg-positive patients (87.8% vs 44.4%). AEs were typical of those associated with PEG-IFN α -2a.

In naïve Korean HBeAg-positive CHB patients treated with PEG-IFN α -2a, higher rates of HBV DNA suppression and HBeAg seroconversion were achieved in the 48-week treatment group than in the 24-week treatment group without additional risk of AEs.

(*Medicine* 95(14):e3026)

Abbreviations: AE = adverse event, ALT = alanine transaminase, anti-HBe = antibody to HBeAg, anti-HBs = antibodies to HBsAg, CHB = chronic hepatitis B, CTCAE = Common Terminology Criteria for Adverse Events, ET = end of treatment, HBeAg = hepatitis B virus endogenous antigen, HBsAg = hepatitis B virus surface antigen, HBV = hepatitis B virus, NA = nucleos(t)ide analogs, PEG-IFN α -2a = pegylated interferon alpha-2a, PT6 = 6 months posttreatment, SAE = serious adverse event, UNL = upper normal limit, VR = virological response.

INTRODUCTION

Chronic hepatitis B (CHB) infection is a global health problem affecting approximately 300 million people worldwide and also a major concern in Asian countries including Korea.¹ As CHB is associated with fatal complications such as cirrhosis, liver failure, and hepatocellular carcinoma, effective therapy is necessary.^{2,3} Currently, there are 2 treatment options for CHB patients: pegylated interferon (PEG-IFN) or oral nucleos(t)ide analogs (NA).⁴ The advantage of PEG-IFN over NA is the dual action of immune-modulation and antiviral effects, which together result in a relatively high chance of achieving hepatitis B virus surface antigen (HBsAg) clearance in patients with undetectable HBV DNA.^{5,6} However, PEG-IFN has several drawbacks when compared to NAs, including lower potency for viral suppression, inconvenient administration, and several side effects.⁴

Editor: Maohua Xie.

Received: September 21, 2015; revised: February 10, 2016; accepted: February 13, 2016.

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This study was supported by partial research grants from F Hoff mann-La Roche (Korea).

The authors have no conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000003026

For this reason, PEG-IFN has been used in only a small number of highly selected patients. Therefore, efficacy and safety data based on treatment experiences in Korea are lacking. Although there is one published study showing the efficacy and safety of PEG-IFN α -2a in Korean patients with CHB, the study included only a small number of patients ($n = 88$).⁷ In addition, even worldwide, only a few small studies have investigated the proper dose and duration of PEG-IFN α -2a treatment in patients with CHB.^{8–10} Recently, after publication of the NEPTUNE study,¹¹ all guidelines are recommending the use of PEG-IFN α -2a 180 μ g for 48 weeks in hepatitis B virus endogenous antigen (HBeAg) positive patients as well as in HBeAg-negative patients.^{4,12} However, there has been no study validating the result that PEG-IFN α -2a 180 μ g for 48 weeks is superior over 24 weeks of treatment in a Korean patient cohort.

Thus, this study aimed to investigate the efficacy and safety of PEG-IFN α -2a in Korean patients with CHB who are receiving the treatment in a real life setting. Specifically, we compared treatment responses (hepatitis B virus [HBV] DNA suppression, virological response [VR], HBsAg seroconversion, HBeAg seroconversion in HBeAg-positive patients, alanine transaminase [ALT] normalization) between the 24- and 48-week regimens at the end of treatment (ET) and at 6 months posttreatment (PT6). We also evaluated adverse events (AEs) and serious adverse events (SAEs).

MATERIALS AND METHODS

Patients

From May 2005 to May 2011, 640 patients who showed HBV DNA > 20000 IU/mL in HBeAg-positive patients and HBV DNA > 2000 IU/mL in HBeAg-negative patients and who were being treated with PEG-IFN α -2a as the first-line therapy in 18 Korean hospitals were considered for inclusion in this cohort study. In practice, treatment regimens with PEG-IFN α -2a 180 μ g/week are usually either 24 or 48 weeks long based upon the clinician's decision and factors such as the patients' VR and clinical condition, safety, and medical insurance. Exclusion criteria were as follows: patients with other concurrent chronic hepatitis (hepatitis C, hepatitis D, autoimmune, or heavy alcoholic liver disease) or human immunodeficiency virus positivity ($n = 5$), patients with previous interferon or oral NA therapy ($n = 30$), patients with no available DNA level was available at the beginning, end, or PT6 ($n = 68$), patients who were lost to follow-up ($n = 10$), and patients who discontinued treatment during the intended treatment period ($n = 88$, AEs [$n = 30$]; patient refusal [$n = 28$]; unknown causes [$n = 18$]; and suboptimal response [$n = 12$]). After excluding 201 patients, data from 439 patients was analyzed (Figure 1). For the safety analysis, a total of 527 patients were analyzed, including

patients who were lost to follow-up ($n = 10$), who discontinued treatment ($n = 88$), and who were in the final cohort ($n = 439$).

This study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from each patient. The institutional review boards of each institute approved this study.

Laboratory Assay and Definitions

Complete blood count, HBeAg, antibody to HBeAg (anti-HBe), HBV DNA, and ALT levels were checked at baseline and every 4 to 12 weeks until the ET and at PT6. HBV DNA levels were quantified using the PCR assay of each respective institute; however, detection limits varied from 5 to 20 IU/mL. HBV DNA suppression was defined as serum HBV DNA less than 2000 IU/mL and VR was defined as serum HBV DNA less than 20 IU/mL, both of which were assessed at ET and PT6. For defining normalization of ALT levels, a threshold of 40 IU/L was used as the upper normal limit (UNL). HBeAg seroconversion was defined as the loss of HBeAg with the development of anti-HBe on at least 2 consecutive follow-up evaluations. HBsAg seroconversion was defined as the loss of HBsAg with the development of antibodies to HBsAg (anti-HBs). AE was defined as any abnormal physical sign, symptom, or disease associated with the patients' treatment with PEG-IFN based on Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0., and SAE was defined as any AE that resulted in death, was life-threatening, required prolonged hospitalization, or caused persistent and significant disability or incapacity. In case of laboratory abnormalities (ie, ALT elevation, neutropenia, or thrombocytopenia), PEG-IFN was reduced in dosage or discontinued depending upon the clinicians' decisions.

Study Endpoints

Treatment responses at ET and PT6 were compared between patients who were treated for 24 weeks versus 48 weeks. The primary endpoint was HBV DNA suppression at ET. The secondary endpoints included VR, HBsAg seroconversion, HBeAg seroconversion in HBeAg-positive patients, ALT normalization, and the development of AEs and SAEs.

Statistical Analysis

Data are expressed as means \pm SD or medians (range) as appropriate. To compare the parameters between groups, the Student t test was used for continuous variables and the χ^2 test was used for categorical variables. Univariate regression analyses were performed to evaluate the predictive factors for HBV DNA suppression at ET. Then, a multivariate regression analysis was performed using factors found to be significant by univariate analysis.

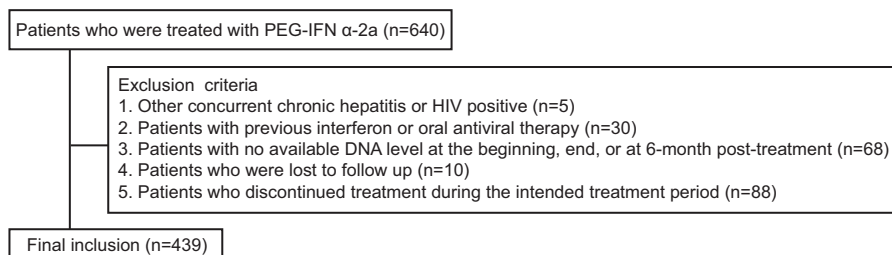


FIGURE 1. Study population. Among 640 patients who were being treated with PEG-IFN α -2a in 18 Korean hospitals, 201 patients were excluded, and data from 439 patients was analyzed.

TABLE 1. Baseline Characteristics

Variables	Total (n = 439)	HBeAg Positive (n = 349)	HBeAg Negative (n = 90)	P
Age, y	38.3 ± 9.3	37.5 ± 9.1	41.5 ± 9.5	<0.001
Male	251 (57.2)	194 (55.6)	57 (63.3)	NS
Treatment duration (wk)				
24	106 (24.1)	90 (25.8)	16 (17.8)	NS
48	333 (75.9)	259 (74.2)	74 (82.2)	
Liver cirrhosis	23 (5.2)	15 (4.3)	8 (8.9)	NS
HBV DNA, log ₁₀ IU/mL	7.85 ± 8.56	7.95 ± 8.61	6.68 ± 7.36	<0.001
ALT, IU/L	138.9 ± 174.5	151.4 ± 189.9	90.6 ± 76.8	<0.001
Albumin, g/dL	4.3 ± 0.5	4.3 ± 0.5	4.2 ± 0.5	NS
Total bilirubin, mg/dL	0.9 ± 0.5	0.9 ± 0.5	0.8 ± 0.3	NS
Prothrombin time, INR	1.1 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	NS

ALT = alanine transaminase, HBeAg = hepatitis B virus endogenous antigen, HBV = hepatitis B virus, INR = international normalized ratio, NS = not significant.

Variables are expressed as mean ± SD (range) or n (%).

Data analysis was performed using SAS software version 18.0 (SAS Institute, Cary, NC) and 2-sided *P* values < 0.05 were considered significant.

RESULTS

Baseline Characteristics

The baseline characteristics of the 439 patients who finished the PEG-IFN α -2a for the intended treatment period are summarized in Table 1. Three hundred forty-nine (79.5%) patients were HBeAg positive, and the other 90 (20.5%) patients were HBeAg negative. The mean age was 38 years and 57.2% of patients were male. Seventy-six percent of patients were treated for 48 weeks and 5.2% of patients had liver cirrhosis. Among the 349 patients with HBeAg positivity, 90 (25.8%) patients were treated for 24 weeks and 259 (74.2%) patients were treated for 48 weeks. Among patients who showed HBeAg negativity (n = 90), 16 (17.8%) patients were treated for 24 weeks and 74

(82.2%) patients were treated for 48 weeks. HBV DNA and ALT level were significantly higher in HBeAg-positive patients than in HBeAg-negative patients (HBV DNA; 7.95 ± 8.61 vs 6.68 ± 7.36 log₁₀IU/mL; *P* < 0.001, ALT; 151.4 ± 189.9 vs 90.6 ± 76.8 U/L; *P* < 0.001).

Efficacy Analysis

Response rates at ET and PT6 are depicted in Tables 2 and 3, respectively. In HBeAg-positive patients, HBV DNA suppression at ET was significantly greater in the 48-week treatment group compared to the 24-week treatment group (44.4% vs 36.7%, *P* = 0.035) (Figure 2A). VR at ET was also better achieved in patients who underwent the longer treatment regimen (48 weeks vs 24 weeks; 22.0% vs 11.1%, *P* = 0.029). At PT6, the HBV DNA suppression rate and VR decreased compared to ET, however, the 48-week treatment group showed significantly higher rates in these parameters than the 24-week treatment group (HBV DNA suppression, 35.9% vs 13.3%,

TABLE 2. Comparison of Response Rates Between 24 Weeks Versus 48 Weeks of Treatment at the End of Treatment

Responses	HBeAg Positive (n = 349)			HBeAg Negative (n = 90)		
	24 wk (n = 90)	48 wk (n = 259)	<i>P</i>	24 wk (n = 16)	48 wk (n = 74)	<i>P</i>
HBV DNA suppression (HBV DNA < 2000 IU/mL)	33 (36.7)	115 (44.4)	0.035	13 (81.2)	65 (87.8)	NS
VR (HBV DNA < 20 IU/mL)	10 (11.1)	57 (22.0)	0.029	8 (50.0)	45 (60.8)	NS
HBeAg loss/seroconversion*	3 (3.3)/2 (2.2)	58 (22.4)/47 (18.1)	<0.001	-	-	
HBsAg loss	0 (0)	1 (0.4)	NS	0 (0)	1 (1.4)	NS
ALT normalization (40 IU/L)	39 (43.3)	148 (57.1)	0.005	6 (37.5)	45 (67.2)	0.039
All of HBV DNA suppression, ALT normalization, HBeAg seroconversion*	2 (2.2)	26 (10.0)	<0.001	5 (31.3)	35 (47.3)	NS
All of VR, ALT normalization, HBeAg seroconversion*	2 (2.2)	16 (6.2)	0.002	3 (18.7)	30 (40.5)	NS

* HBeAg seroconversion was assessed only in patients with HBeAg positive.

ALT = alanine transaminase, HBeAg = hepatitis B virus endogenous antigen, HBsAg = hepatitis B virus surface antigen, HBV = hepatitis B virus, NS = not significant, VR = virological response.

TABLE 3. Comparison of Response Rates Between 24 Weeks Versus 48 Weeks of Treatment at 6 Months Posttreatment

Responses	HBeAg Positive (n = 349)			HBeAg Negative (n = 90)		
	24 wk (n = 90)	48 wk (n = 259)	P	24 wk (n = 16)	48 wk (n = 74)	P
HBV DNA suppression (HBV DNA < 2000 IU/mL)	12 (13.3)	93 (35.9)	0.035	9 (56.3)	35 (47.3)	NS
VR (HBV DNA < 20 IU/mL)	8 (8.9)	36 (13.9)	0.004	2 (12.5)	15 (20.3)	0.044
HBeAg loss/seroconversion*	9 (10.0)/9 (10.0)	81 (31.3)/75 (29.0)	<0.001	-	-	-
HBsAg loss	0 (0)	2 (0.8)	NS	0 (0)	1 (1.4)	NS
ALT normalization (< 40 U/L)	45 (50.0)	85 (71.4)	0.008	7 (43.8)	53 (71.6)	0.041
All of HBV DNA suppression, ALT normalization, HBeAg seroconversion*	4 (4.4)	5 (13.5)	0.002	4 (25.0)	27 (36.5)	NS
All of VR, ALT normalization, HBeAg seroconversion*	4 (4.4)	12 (4.6)	NS	2 (12.5)	13 (17.6)	NS

*HBeAg seroconversion was assessed only in patients with HBeAg positive.

ALT = alanine transaminase, HBeAg = hepatitis B virus endogenous antigen, HBsAg = hepatitis B virus surface antigen, HBV = hepatitis B virus, NS = not significant, VR = virological response.

$P = 0.035$; VR, 13.9% vs 8.9%, $P = 0.004$). The HBeAg seroconversion rate at ET of 18.1% in the 48-week treatment group was significantly higher than the 2.2% ($P < 0.001$) that occurred in the 24-week treatment group. This finding also continued at PT6 (29.0% vs 10.0%, $P < 0.001$). ALT normalization was also significantly higher in the 48-week treatment group compared to the 24-week treatment group at both ET and PT6 (ET, 57.1% vs 43.3%, $P = 0.005$; PT6, 71.4% vs 50.0%, $P = 0.008$). Collectively, the rate of achieving all targets, namely HBV DNA suppression, ALT normalization, and HBeAg seroconversion, at ET and PT6 was higher in the longer treatment group (48 weeks vs 24 weeks; at ET, 10.0% vs 2.2%; $P < 0.001$; at PT6, 13.5% vs 4.4%; $P = 0.002$). HBsAg loss was present in only 1 (0.4%) patient at ET and 2 patients (0.8%) at PT6 in the 48-week treatment group. In contrast, no patients achieved HBsAg loss at any time point in the 24-week treatment group.

Following 48 weeks of treatment in HBeAg-negative patients, HBV DNA suppression and VR at ET was higher

than in HBeAg-positive patients (HBeAg-negative vs HBeAg positive; HBV DNA suppression, 87.7% vs 44.4%; VR, 60.8% vs 22.0%). In HBeAg-negative patients at ET, 48-week treatment group compared to 24-week treatment group, did not show statistically superior treatment responses in terms of HBV DNA suppression (87.8% vs 81.2%, $P = 0.780$) (Figure 2B) and VR (60.8% vs 50.0%, $P = 0.437$). Only the ALT normalization rate at ET was significantly higher in the 48-week treatment group compared to the 24-week treatment group (67.2% vs 37.5%, $P = 0.039$). At PT6, HBV DNA suppression was similar between 24-week treatment group and 48-week treatment group (56.3% vs 47.3%, $P = 0.435$). VR (20.3% vs 12.5%, $P = 0.044$), and ALT normalization (71.6% vs 43.8% $P = 0.041$) were significantly greater in the 48-week treatment group compared to the 24-week treatment group. In HBeAg-negative patients, only 1 (1.4%) patient in the 48-week treatment group showed HBsAg loss during the treatment period and at the PT6 time point.

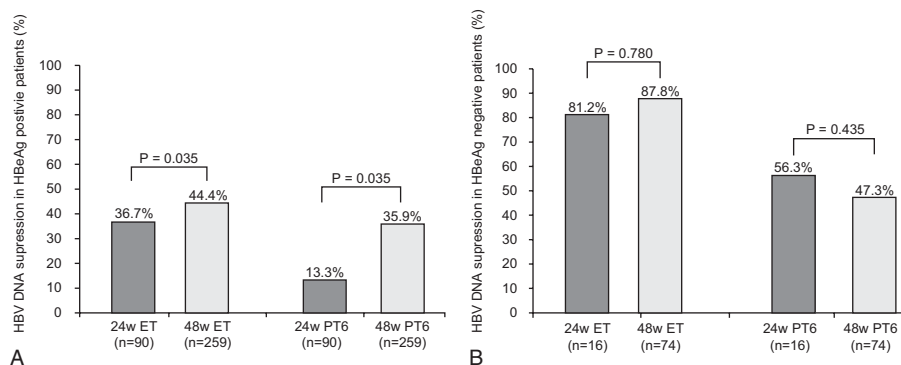


FIGURE 2. HBV DNA suppression according to treatment length at the end of treatment and at 6 months posttreatment in (A) HBeAg-positive patients and (B) HBeAg-negative patients. (A) In HBeAg-positive patients, HBV DNA suppression at ET and PT6 was significantly greater in the 48-week treatment group compared to the 24-week treatment group (at ET, 44.4% vs 36.7%, $P = 0.035$; at PT6, 35.9% vs 13.3%, $P = 0.035$). (B) In HBeAg-negative patients, 48-week treatment group compared to 24-week treatment group, did not show statistically superior treatment responses in terms of HBV DNA suppression (at ET, 87.8% vs 81.2%, $P = 0.780$; at PT6, 47.3% vs 56.3%, $P = 0.435$). ET, end of treatment; PT6, 6 months posttreatment.

TABLE 5. Safety Profiles of Pegylated Interferon α -2a

Variables	Total (n = 527)	HBeAg Positive (n = 422)			HBeAg Negative (n = 105)		
		24 wk (n = 100)	48 wk (n = 322)	P	24 wk (n = 19)	48 wk (n = 86)	P
Total patients with ≥ 1 AE	99 (18.8)	20 (20.0)	50 (15.5)	NS	5 (26.3)	24 (27.9)	NS
Total AEs	108 (20.5)	20 (20.0)	55 (17.1)	NS	5 (26.3)	28 (32.6)	NS
Pyrexia	24 (4.6)	5	12		1	6	
Fatigue	20 (3.8)	2	16		0	2	
Myalgia	19 (3.6)	4	9		2	4	
Alopecia	10 (1.9)	3	4		0	3	
Insomnia	8 (1.5)	1	3		1	3	
Rash	8 (1.5)	2	4		0	2	
Headache	7 (1.3)	2	3		0	2	
Depression	5 (0.9)	1	1		0	3	
Arthralgia	4 (0.8)	0	2		0	2	
Gastrointestinal discomfort	2 (0.4)	0	1		1	0	
Respiratory difficulty	1 (0.2)	0	0		0	1	
Laboratory abnormalities	62 (11.8)	10 (10.0)	35 (10.9)	NS	4 (21.0)	13 (15.1)	NS
ALT elevation ($>5 \times$ UNL)	10 (1.9)	2 (2.0)	7 (2.2)	NS	1 (5.2)	0 (0)	NS
Neutropenia ($<750/\text{mm}^3$) or Thrombocytopenia ($<50,000/\text{mm}^3$)	52 (9.9)	8 (8.0)	28 (8.7)	NS	3 (15.8)	13 (15.1)	NS

AE = adverse event, ALT = alanine transaminase, HBeAg = hepatitis B virus endogenous antigen, NS = not significant, UNL = upper normal limit.

DISCUSSION

To date, PEG-IFN is accepted as a first-line drug for the treatment of naïve CHB patients because it has both direct antiviral activity and immunomodulatory action.⁵ Recently, all international guidelines have adopted the results of a large clinical trial (the NEPTUNE study), which proved that antiviral efficacy was maximized when PEG-IFN α -2a 180 $\mu\text{g}/\text{week}$ was given for 48 weeks.^{4,12} However, in general, the outcomes of HBV treatment from “real-life” situations are believed to be different from those derived from large clinical trials because clinical practice involves various conditions including attenuated monitoring and poor compliance due to individual circumstances. Our present study validated the efficacy of PEG-IFN α -2a in a “real-life” setting and specifically investigated the appropriateness of 180 $\mu\text{g}/\text{week}$ dosing and 48 week treatment periods in Korean naïve CHB patients. In addition, this study monitored certain key side effects of PEG-IFN α -2a that often cause clinicians and patients to hesitate when first considering its use. This multicenter study provided valuable insights regarding PEG-IFN therapy in Korean naïve CHB patients in a real clinical setting.

In HBeAg-positive patients, HBV DNA suppressions (HBV DNA < 2000 IU/mL) at ET and PT6 after 48 weeks of treatment, were 44.4% and 35.9%, respectively. Although direct comparison is difficult, these “real-life” results are comparable with those from a well-controlled phase III clinical trial by Lau et al⁹ (HBV DNA $< 100,000$ copies/mL; 52.0% at ET and 32.0% at PT6). HBeAg loss was also comparable between the 2 studies (this study vs Lau et al; 22.4% vs 27.0% at ET; 29.0% vs 32.0% at PT6). Contrary to the results of previous literature, which indicated that genotype C or B HBV is associated with poorer outcomes than genotype A HBV,¹³ treatment response rates in our Korean HBeAg-positive patients who were exclusively infected with genotype C HBV were not

inferior to another large study by Lau et al, which enrolled 80% non-Asians with predominantly genotype A or D HBV. Moreover, HBeAg seroconversion and HBV DNA suppression rates in our study were not inferior to another large study by Janssen et al,¹⁴ which enrolled 80% non-Asians with predominantly genotype A or D HBV. When treatment periods (48 weeks vs 24 weeks) were compared in our study, outcomes at ET in terms of HBV DNA suppression, HBeAg loss/seroconversion, ALT normalization, and combined response were all significantly greater in the 48-week treatment group than in the 24-week treatment group. This tendency toward higher response rates with longer treatment time was also maintained at PT6. All of the above findings awaken expectations to follow the protocol of the NEPTUNE study¹¹ and to use PEG-IFN α -2a at a dose of 180 $\mu\text{g}/\text{week}$ for 48 weeks in the treatment of Korean HBeAg-positive CHB patients.

In HBeAg-negative patients, HBV DNA suppression was well achieved at ET after 48 weeks of treatment and this result was sustained at PT6. HBV DNA suppression after 48 weeks of treatment (87.8% at ET; 47.3% at PT6) was comparable to results seen in a large clinical trial by Marcellin et al¹⁰ (HBV DNA $< 20,000$ copies/mL; at ET, 81.0%; at PT6, 43.0%) and a previous study by Kwon et al,⁷ which included a small number of Koreans (HBV DNA < 2000 IU/mL; at ET, 71.4%; at PT6, 47.6%). In terms of HBV DNA suppression at ET and at PT6, 48-week treatment group showed similar results to 24-week treatment group. Considering the small number of sample size in HBeAg-negative patients, comparison of efficacy analyses between 48 and 24-week treatment of PEG-IFN α -2a in Korean HBeAg-negative CHB patients should be investigated in the future study.

The HBeAg seroconversion rate further increased during the 6 months after stopping treatment (2.2–10.0% in the 24-week treatment group, 18.1–29.0% in the 48-week

treatment group), suggesting high durability of PEG-IFN. In a large study by Buster et al,⁵ HBeAg negativity was sustained for 3 years in 81% patients who showed HBeAg negativity at 24 weeks post-PEG-IFN treatment. Similarly, in HBeAg-negative patients, the biochemical and VR were sustained for 3 years in approximately 25% of patients who were given a 48-week course of PEG-IFN α -2a.¹⁵ In short, PEG-IFN α -2a provided a more favorable sustained posttreatment response than NA, probably due to the drug's off-treatment immune control over HBV.¹⁶ Moreover, the HBsAg clearance that is induced by PEG-IFN therapy will be associated with long-term complication-free survival,¹⁵ supporting the use of PEG-IFN α -2a therapy as a primary option for the treatment CHB patients.

However, antiviral efficacy of PEG-IFN in terms of HBV DNA suppression is moderate compared to that of third generation NAs such as ETV^{17–19} or TDF^{20–22} (VR at week 48 in naïve HBeAg-negative patients treated with ETV, 88–99%; TDF, 89–95%; VR at week 48 in naïve HBeAg-positive patients treated with ETV, 48–75%; TDF, 59–76%). In addition, uncomfortable subcutaneous injection and frequent need of laboratory monitoring made clinicians to use PEG-IFN only for selected patients. The desire to determine which patients would derive the most benefit from PEG-IFN α -2a therapy drove clinicians to investigate predictors for favorable VR. In HBeAg-negative patients, a study by Bonino et al²³ showed high baseline ALT, low baseline HBV DNA, younger age, female gender, and genotype B or C rather than genotype D as independent predictors of a combined ALT and HBV DNA response at 24 weeks posttreatment. In the PARC trial, which included 102 genotype D dominant HBeAg-negative CHB patients, no decline in HBsAg level plus no reduction in HBV DNA $\geq 2 \log_{10}$ level at week 12 was established as a stopping rule for PEG-IFN α -2a therapy²⁴; this criteria was also externally validated in subsequent studies.^{25,26} In HBeAg-positive patients, low baseline HBV DNA, the presence of the precore G1896A mutation or the basal core promoter A1762T/G1764A mutation,²⁷ and HBV genotype B rather than genotype C,²⁸ are known to be associated with good PEG-IFN response. In addition, declines in HBsAg and HBeAg levels have also been reported as on-treatment predictors.^{29,30} In our study, baseline low HBV DNA, high ALT level, and low HBV DNA at week 12 ($< 2 \log_{10}$ IU/mL) turned out to be significant predictors for achieving HBV DNA suppression at ET in Korean HBeAg-positive patients. Thus, HBV DNA and ALT should be measured before treatment and taken into account when considering the initiation of PEG-IFN. Also, HBV DNA at week 12 should be checked and factored into the decision of whether to continue therapy. In our study, 82.3% (28 of 34) of patients who did not achieve HBV DNA suppression after completion of PEG-IFN therapy and started entecavir achieved VR within 1 year, suggesting the possible effectiveness of sequential PEG-IFN and NA treatment. In a study by Iannazzo et al,³¹ the cost-effectiveness of applying the 12-week HBV DNA/HBsAg stopping rule for PEG-IFN therapy in HBeAg-negative CHB and switching to an effective NA treatment was demonstrated. The effectiveness of response-guided first-line treatment with PEG-IFN followed by a switch to NA, which enables individualized treatment for CHB, should be further validated in future studies.

Regarding safety, there was no difference between the 48-week treatment group and the 24-week treatment group in the total number or the character of AEs, suggesting that the 48-week PEG-IFN treatment was not only more efficient but also carried no increased risk of AEs in Koreans. No SAE was

reported up to 6 months after treatment in our study cohort. Compared with studies that included patients of various races, the prevalence of AE and the proportion of moderate to severe laboratory abnormalities were lower in Koreans, suggesting that Koreans may tolerate the PEG-IFN-based treatment better than patients in other race groups.^{9,10,14,32} However, the profile of AE was similar between our study and other studies and systemic symptoms such as pyrexia, fatigue, and myalgia were the most common complaints.^{9,10,14,32}

This study has several limitations, which are delineated as follows: As this is a retrospective, multicenter study, many applicants were lost during enrollment and follow-up. In addition, these data did not reflect the typical response rates and safety profile of that have been seen in primary and secondary hospitals of Korea. However, this study is the largest study that enrolled many homogenous Korean CHB patients with genotype C and demonstrated efficacy and safety in a real-life setting during the designated follow-up period of PT6. Therefore, it is our hope that future studies will investigate the same primary and secondary endpoints during extended follow-up periods as well as the clinical course and treatment options for patients with virological breakthrough after PEG-IFN treatment.

In conclusion, the efficacy and the safety of PEG-IFN in a real-world situation were equivalent to results seen in clinical trials. In addition, higher HBV DNA suppression was achieved in the 48-week treatment group than in the 24-week treatment group without additional risk of AEs in HBeAg-positive CHB patients. However, considering the moderate efficacy of PEG-IFN α -2a in terms of direct viral suppression, PEG-IFN α -2a should be carefully applied to selected naïve Korean CHB patients. Pretreatment and on-treatment predictors such as baseline HBV DNA, baseline ALT level, or HBV DNA during treatment will allow individualization of therapy and should be further validated in the future in order to maximize beneficial patient outcomes.

ACKNOWLEDGMENTS

The authors are grateful to Prof. Do young Kim and Prof. Seung Up Kim from Yonsei University for their help in enrollment of subjects. We also appreciate Dong-Su Jang (Medical Illustrator, Medical Research Support Section, Yonsei University College of Medicine, Seoul, Korea) for his help with the figures.

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