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The Efficacy and Safety of Peginterferon-α-2a in Korean Patients with Chronic Hepatitis B: A Multicenter Study Conducted in a Real Clinical Setting

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Background/Aims: Genotype C is the principal type of hepatitis B virus (HBV) in Koreans and is associated with poor prognosis for peginterferon α-2a therapy. The efficacy of and compliance to peginterferon α-2a therapy were investigated in Koreans with hepatitis B in a real clinical setting. **Methods:** Hepatitis B patients treated with peginterferon α-2a from 2008 to 2011 at four university hospitals were consecutively enrolled. **Results:** Eighty-eight patients were enrolled; 67 were hepatitis B e antigen (HBeAg)-positive. The mean treatment period was 36.1±15.2 weeks. In 26.1% of patients, treatment was discontinued due to insufficient antiviral effects and adverse events. At 24 weeks after treatment, 10/42 (23.8%) HBeAg-positive patients achieved both HBV DNA suppression to <2,000 IU/mL and HBeAg loss/seroconversion. For HBeAg-negative patients, 10/13 (76.9%) achieved HBV DNA suppression to <2,000 IU/mL at 24 weeks after treatment. During the follow-up period, 15 (30.6%) of the 49 patients who achieved HBV DNA suppression to 2,000 IU/mL developed a breakthrough HBV DNA level of $>2\times10^6$ IU/mL. **Conclusions:** Peginterferon α-2a therapy in Koreans with hepatitis B in a real clinical setting resulted in a lower virologic response, as compared to Western individuals, but a favorable durability. There is a need to reduce the high rate of premature discontinuation compared to the controlled studies. **(Gut Liver 2013;7:197-205)**

Key Words: Peginterferon; Chronic hepatitis B; Asian continental ancestry group

INTRODUCTION

Chronic hepatitis B (CHB) can be managed with effective antiviral agents, but hepatitis B virus (HBV) infection remains a common cause of death from liver disease. Oral nucleos(t)ide analogue agents rapidly suppress HBV DNA levels, and treatment with peginterferon (pegylated interferon, PEG-IFN) α-2a results in hepatitis B surface antigen (HBsAg) clearance in some patients and shows antiviral effects as well as immune-modulatory effects.

However, the efficacy of PEG-IFN α-2a is limited to a small percentage of selected patients. High levels of pretreatment alanine aminotransferase (ALT) and low levels of serum HBV DNA are known to be the most important predictors of response.[1,2] In trials in Asian patients with hepatitis B e antigen (HBeAg)-positive CHB, response in patients with a normal ALT level was poor, but response in patients with an elevated ALT level was similar to that reported in Caucasian patients.[2] Genotype C is the principal type of HBV in Koreans[3,4] and is known to be associated with lower rates of HBeAg seroconversion than genotype A or B.[2,5,6] Furthermore, interferon therapy is not as potent as oral nucleos(t)ide agents at achieving viral suppression, is less convenient to use, and is associated with several side effects. Regarding costs, Korea Health Insurance supports only 24 weeks of PEG-IFN α-2a therapy in HBeAg positive patients and 48 weeks of therapy in HBeAg negative patients.

As a result, there is little experience of PEG-IFN α-2a therapy in Koreans with CHB.[7] The findings of several well-controlled

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large scale trials suggest that PEG-IFN α-2a is both effective and safe for the treatment of CHB,[5,8,9] but the clinicians still wonder about its effectiveness, the rate of discontinuation, and adverse events in the clinical setting. Therefore, we analyzed a multicenter data on PEG-IFN α-2a experiences in Korean patients with CHB and analysed its effectiveness, safety, and patient compliance in real clinical settings.

MATERIALS AND METHODS

1. Study populations

We retrospectively collected the data of CHB patients treated with PEG-IFN α-2a from 2008 (when PEG-IFN α-2a was first introduced in Korea) to 2011 at four tertiary university hospitals. In general, Korean doctors prescribed 48 weeks of PEG-IFN α-2a in HBeAg-negative patients but in HBeAg-positive patients, 24 or 48 weeks were prescribed based on clinician's decision regarding adverse events and the degree of on-treatment virologic response. Treatment discontinuation was defined as the premature stopping of PEG-IFN before completing the clinician's first intended treatment periods, which correspond to 24 weeks or 48 weeks in HBeAg-positive patients and 48 weeks in HBeAg-negative patients.

All enrolled patients were ethnic Koreans and their genotypes were not checked because almost Korean patients were genotype C.[3,4] Patients were excluded if they had any evidence of autoimmune hepatitis, metabolic liver disease, heavy alcohol abuse or markers of hepatitis C virus, hepatitis D virus, or HIV, and pregnancy. Previous oral antiviral drug treatment for CHB was permitted, but not within the 6 months before the study. The study protocol was approved by the review board at each participating institution.

2. Laboratory analyses

Laboratory checks were generally conducted from baseline and 4 to 12 week intervals. Serum levels of ALT, HBV DNA, HBeAg, anti-HBe, HBsAg, and anti-HBs were included. All institutions checked HBV DNA concentrations by real time polymerase chain reaction (PCR). However, detection limits varied from 5 to 20 IU/mL at the lower level and from 2×10^6 to 2×10^8 IU/mL at the upper level. HBeAg and HBsAg were measured quantitatively or qualitatively at each institution, and thus HBeAg and HBsAg are described as "positive" or "negative."

According to recent guidelines,[2] a complete virologic response has been defined as a decrease in serum HBV DNA to undetectable levels as determined by real time PCR. However undetectable HBV DNA suppression by PEG-IFN α-2a was less frequently, HBV DNA suppression was defined in two ways, that is, to be less than 2,000 IU/mL or undetectable (<20 IU/mL) of serum HBV DNA.[1,2] In present study, end of treatment response was defined at the end of treatment as HBV DNA level less than 2,000 IU/mL in both HBeAg-positive and -negative patients. Sustained response was defined as both HBeAg loss/seroconversion and HBV-DNA level less than 2,000 IU/mL in HBeAg-positive patients and HBV DNA less than 2,000 IU/mL in HBeAg-negative patients at 24 weeks post-treatment. As the results of end of treatment response and sustained response, three groups were divided. Nonresponder was defined as the patients who failed the end of treatment response and sustained response. Early relapser was defined as the patients who achieved the end of treatment response but failed the sustained response. Sustained responder was defined as the patients who achieved both the end of treatment response and sustained response. Adverse events were assessed and the rate and causes of discontinuation were analysed.

3. Statistical analysis

Data are expressed as means±SDs or as medians and ranges. Statistical analyses were performed using SPSS version 14.0 for Windows (SPSS Inc., Chicago, IL, USA). Baseline variables were compared using the chi-square test and the Mann-Whitney U test. Factors affecting the end of treatment response and sustained response were identified by univariate and multivariate analysis using a logistic regression model.

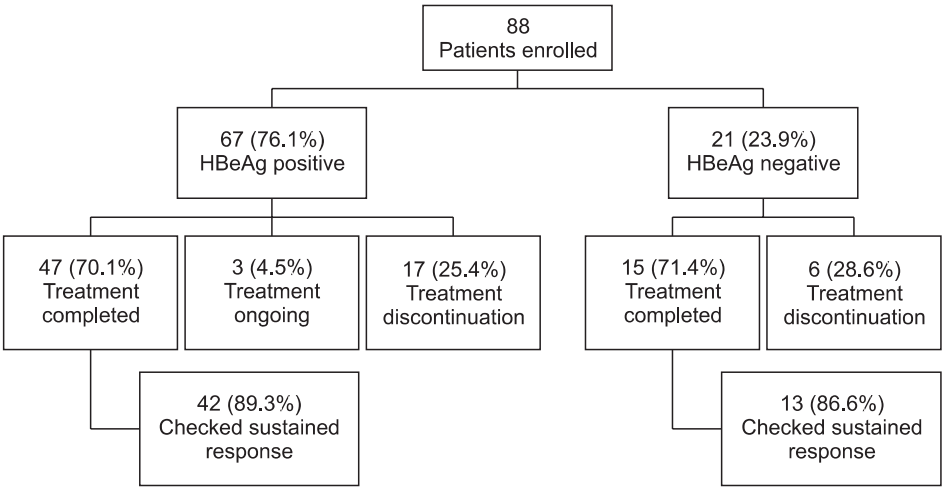

Fig. 1. Patient's flow sheet.
HBeAg, hepatitis B e antigen.

RESULTS

1. Patient demographics

Eighty-eight patients who met the enrollment criteria and were consecutively treatment at the four university hospitals were included (Fig. 1). Sixty-seven patients (76.1%) were HBeAg-positive, and 47 HBeAg-positive patients (70.1%), and 15 HBeAg-negative patients (71.4%) completed intended treatment. The 15.7% of HBeAg-positive patients who completed treatment had been treated for 24 weeks and other patients had been treated for 48 weeks. Finally, 55 patients, followed for 24 weeks after completing therapy, were checked for sustained response. 25.4% (17/67) of HBeAg-positive and 28.6% (6/21) of HBeAg-negative patients prematurely discontinued treatment.

Baseline investigations are described in Table 1. The mean age was 35.1±8.8 years and 56.8% was male patients. Almost patients had been diagnosed with chronic hepatitis. The mean treatment period was 36.1±15.2 weeks and median treatment period in HBeAg-positive patients and -negative patients was not difference (48 weeks vs 48 weeks, respectively; p=0.779). Pretreatment HBV DNA levels in HBeAg-positive patients were significantly higher than those in HBeAg-negative patients. Three out of six patients that had been previously treated with lamivudine agents had confirmed lamivudine resistance mutations.

2. Antiviral response to PEG-IFN α-2a therapy

Virologic, serological, and biochemical responses are de-

Table 1. Baseline Characteristics of the Patients

Characteristic	HBeAg-positive (n=67)	HBeAg-negative (n=21)	Total patients (n=88)	p-value
Age	34.5±9.1	36.9±7.6	35.1±8.8	0.275
Male sex	37 (55.2)	13 (61.9)	50 (56.8)	0.590
Treatment weeks	48 (1–57)	48 (14–52)	48 (1–57)	0.779
Follow-up weeks	69 (13–219)	87 (17–163)	72 (13–219)	0.506
Chronic hepatitis	62 (92.5)	17 (81.0)	79 (89.8)	0.126
Liver biopsy	22 (32.8)	6 (28.6)	28 (31.8)	0.714
Fibrosis score*	2 (0–4)	2 (0–4)	2 (0–4)	0.693
HBV DNA, log IU/mL	5.6 (2.8–8.3)	5.6 (3.1–8.2)	6.7 (2.8–8.3)	0.003
ALT, U/L	190.9±149.2	184.7±151.2	189.4±148.8	0.869
Albumin, g/dL	4.2±0.4	4.4±0.4	4.2±0.4	0.031
Total bilirubin, mg/dL	0.9±0.3	0.8±0.3	0.86±0.3	0.736
Prothrombin time, INR	1.07±0.09	1.05±0.10	1.07±0.09	0.451
Previous treatment	3 (4.5)	3 (14.3)	6 (6.8)	0.141

Data are presented as mean±SD, number (%), or median (range).
HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; INR, international normalized ratio.
*Metavir fibrosis score.

Table 2. Response Rates at the End of Treatment and at 24 Weeks Post-Treatment

	End of treatment response				Sustained response (24 wk posttreatment)			
	HBeAg-positive (ITT, n=67)	HBeAg-negative (ITT, n=21)	HBeAg-positive (PP, n=47)	HBeAg-negative (PP, n=15)	HBeAg-positive (ITT, n=67)	HBeAg-negative (ITT, n=21)	HBeAg-positive (PP, n=42)	HBeAg-negative (PP, n=13)
HBV DNA <2,000 IU/mL	22 (32.8)	15 (71.4)	20 (42.6)	13 (86.7)	11 (16.4)	10 (47.6)	11 (26.2)	10 (76.9)
HBV DNA <20 IU/mL	7 (10.4)	11 (52.4)	7 (14.9)	10 (66.7)	5 (7.4)	4 (19.0)	5 (11.9)	4 (30.8)
HBeAg seroconversion	8 (12.5)		6 (12.8)		9 (13.4)		9 (21.4)	
HBeAg loss	9 (13.4)		7 (14.9)		13 (19.4)		13 (30.9)	
HBV DNA <2,000 IU/mL, HBeAg seroconversion/loss	9 (13.4)		7 (14.9)		10 (14.9)		10 (23.8)	
ALT normalization	32 (47.8)	11 (52.4)	26 (55.3)	9 (60.0)	29 (43.2)	12 (57.1)	29 (69.0)	12 (92.3)

Data are presented as number (%).
HBeAg, hepatitis B e antigen; ITT, intention to treatment analysis; PP, per protocol analysis; HBV, hepatitis B virus; ALT, alanine aminotransferase.

scribed in Table 2. After 12 weeks of therapy, 47.8% of HBeAg-positive patients and 28.6% of HBeAg-negative patients exhibited less than 1 log IU/mL decrease in HBV DNA level from baseline,[10] but treatment maintenance was decided by clinician's judgment.

At the end of therapy, 14.9% and 66.7% of HBeAg-positive patients achieved the HBV DNA suppression undetectable and <2,000 IU/mL, respectively. The 12.8% of patients seroconverted to anti-HBe and 14.9% of patients lost HBeAg. The rate of virologic response in HBeAg-positive patients was significantly lower than in HBeAg-negative patients (p=0.002).

After 24 weeks of therapy, 23.8% of HBeAg-positive patients achieved the sustained response (both the HBeAg loss/seroconversion and viral suppression <2,000 IU/mL). The 11.9% and 26.2% of HBeAg-positive patients achieved the HBV DNA suppression undetectable and <2,000 IU/mL, respectively. At the 24 weeks post-treatment, the rate of HBV DNA <2,000 IU/mL in HBeAg-positive patients was lower than in HBeAg-negative patients (p=0.001), but the HBV DNA undetectable rate was not different between the two groups (p=0.108). Regarding serologic

Table 3. Predictive Factors for the End of Treatment Response by Univariate and Multivariate Analysis

Variable	Total patients (n=62)				HBeAg-positive (n=47)			
	Univariate analysis, OR (95% CI)	p-value	Multivariate analysis, OR (95% CI)	p-value	Univariate analysis, OR (95% CI)	p-value	Multivariate analysis, OR (95% CI)	p-value
Pretreatment factors								
Age <35 yr old	2.221 (0.801–6.155)	0.125	-	-	1.250 (0.326–4.788)	0.745	-	-
Baseline DNA <7 log, IU/mL	2.479 (0.890–6.905)	0.082	-	-	1.250 (0.326–4.788)	0.745	-	-
Baseline ALT >5×UNL	4.518 (1.387–14.715)	0.012	4.007 (0.926–17.345)	0.063	6.667 (1.476–30.106)	0.014	5.289 (1.082–25.866)	0.040
HBeAg-negative	8.775 (1.777–43.335)	0.008	3.422 (0.575–20.387)	0.177	-	-	-	-
On-treatment factors								
12 wk response*	19.5 (5.023–75.703)	0.000	12.020 (2.741–52.720)	0.001	11.667 (2.770–49.130)	0.001	8.043 (1.750–36.961)	0.007
24 wk response†	26.667 (5.905–120.424)	0.000	-	-	17.333 (3.526–85.219)	0.000	-	-
HBeAg seroconversion	-	-	-	-	1.905 (0.550–6.592)	0.309	-	-
48 wk treatment (vs 24 wk)	-	-	-	-	2.206 (0.332–14.635)	0.413	-	-

HBeAg, hepatitis B e antigen; OR, odds ratio; CI, confidence interval; ALT, alanine aminotransferase; UNL, upper normal limit.
*Hepatitis B virus (HBV) DNA level at week 12 less than 5 log IU/mL; †HBV DNA level at week 24 less than 5 log IU/mL.

Table 4. Predictive Factors for a the Sustained Response by Univariate and Multivariate Analysis

Variable	Total patients (n=55)				HBeAg-positive (n=42)			
	Univariate analysis, OR (95% CI)	p-value	Multivariate analysis, OR (95% CI)	p-value	Univariate analysis, OR (95% CI)	p-value	Multivariate analysis, OR (95% CI)	p-value
Pretreatment factors								
Age <35 yr old	2.538 (0.882–7.836)	0.105	-	-	1.667 (0.398–6.974)	0.484	-	-
Baseline DNA <7 log, IU/mL	2.476 (0.794–7.718)	0.118	-	-	1.026 (0.241–4.369)	0.972	-	-
Baseline ALT >5×UNL	1.556 (0.473–5.119)	0.467	-	-	2.000 (0.448–8.936)	0.364	-	-
HBeAg-negative	10.667 (2.446–46.517)	0.002	4.500 (0.851–23.801)	0.077	-	-	-	-
On-treatment factors								
12 wk response*	7.692 (1.854–31.911)	0.005	-	-	4.000 (0.824–19.423)	0.086	-	-
24 wk response†	13.125 (2.554–67.461)	0.002	7.000 (1.180–41.536)	0.032	7.000 (1.180–41.536)	0.032	NA	0.998
HBeAg seroconversion	-	-	-	-	39.000 (4.116–369.510)	0.001	NA	0.997
48 wk treatment (vs 24 wk)	-	-	-	-	1.286 (0.127–13.036)	0.832	-	

HBeAg, hepatitis B e antigen; OR, odds ratio; CI, confidence interval; ALT, alanine aminotransferase; UNL, upper normal limit; NA, not available.
*Hepatitis B virus (HBV) DNA level at week 12 less than 5 log IU/mL; †HBV DNA level at week 24 less than 5 log IU/mL.

response after 24 weeks of therapy, seroconversion rate to anti-HBe increased in 21.4% of patients and loss of HBeAg was exhibited in 30.9% of patients. In more than two thirds of patients, ALT normalization was achieved. There is no one who achieved seroconversion or loss of HBsAg during the whole period.

In the HBeAg-negative patients, 66.7% and 86.7% of patients achieved the HBV DNA suppression undetectable and <2,000 IU/mL, respectively at the end of therapy. However, at the 24 weeks post-treatment, only 30.8% and 76.9% of HBeAg-negative patients showed the HBV DNA suppression undetectable and <2,000 IU/mL, respectively.

The serum ALT level (>5×upper normal limit) and HBeAg negativity at baseline were found to be good pretreatment predictors of end of treatment response (Table 3). In addition, HBV DNA level less than 5 log IU/mL at week 12 and 24 were found to be favorable predictors. Multivariate analysis for the end of treatment response showed that HBV DNA level less than 5 log IU/mL at week 12 were significant factors in all patients and HBeAg-positive patients.

In terms of predicting sustained response, HBeAg negativity was found to be good pretreatment factors (Table 4). Also, less than a 5 log of HBV DNA level at week 24 and seroconversion to anti-HBe were found to be on-treatment predictors in HBeAg-positive patients. By multivariate analysis for sustained response, less than a 5 log of HBV DNA level at week 24 was the only significant factor in all patients. There was no consistent predictor of end of treatment response or sustained response in each HBeAg-positive and -negative patients.

3. Serial changes in HBV DNA level

Fig. 2A shows mean HBV DNA concentrations during treatment and follow-up period in patients who completed therapy. Serial HBV DNA levels at each time points within the treatment period in the nonresponder were significantly higher than those in the sustained responder and early relapser ($p<0.005$), except at baseline. However, serial HBV DNA levels within the treatment period could not discriminate between the early relapser and sustained responder. Both the early relapser and sustained responder exhibited good HBV DNA suppression during treatment period although HBV DNA levels at 6 months or later in the early relapser were higher than those in the sustained responder. Fig. 2B exhibited the difference of serial HBV DNA levels between HBeAg-positive and -negative patients. On-treatment HBV DNA levels in the HBeAg-negative patients were lower than those in the HBeAg-positive patients from baseline to week 48 of treatment. However, off-treatment HBV DNA levels were not different between HBeAg-positive patients and -negative patients because a number of HBeAg-negative patients relapsed.

4. Durability of viral and serological responses

During the whole follow-up period (72 weeks; range, 13 to 219 weeks) including treatment period, 47.8% (32/67) of HBeAg-positive patients and 81.0% (17/21) of HBeAg-negative patients exhibited HBV DNA suppression <2,000 IU/mL ($p=0.008$). Time to suppression of HBV DNA (<2,000 IU/mL) in HBeAg-positive patients took much longer than in HBeAg-negative patients (median, 431 days [range, 90 to 771 days] vs 37 days [range, 26 to 48 days]; $p=0.000$) (Fig. 3A). Among the patients who achieved the suppression of HBV DNA <2,000 IU/mL, 40.6% (13/32) of HBeAg-positive patients and 11.8% (2/17) of HBeAg-negative patients showed HBV DNA relapse $>2\times10^6$ IU/mL 333 days (range, 28 to 604 days) after suppression of HBV DNA <2,000 IU/mL (Fig. 3B). However, 42.8% of the relapsers could maintain the ALT normalization during the follow-up period without the additional antiviral agents.

During the whole follow-up period, HBeAg seroconversion developed in 26.9% (18/67). Median time to HBeAg seroconver-

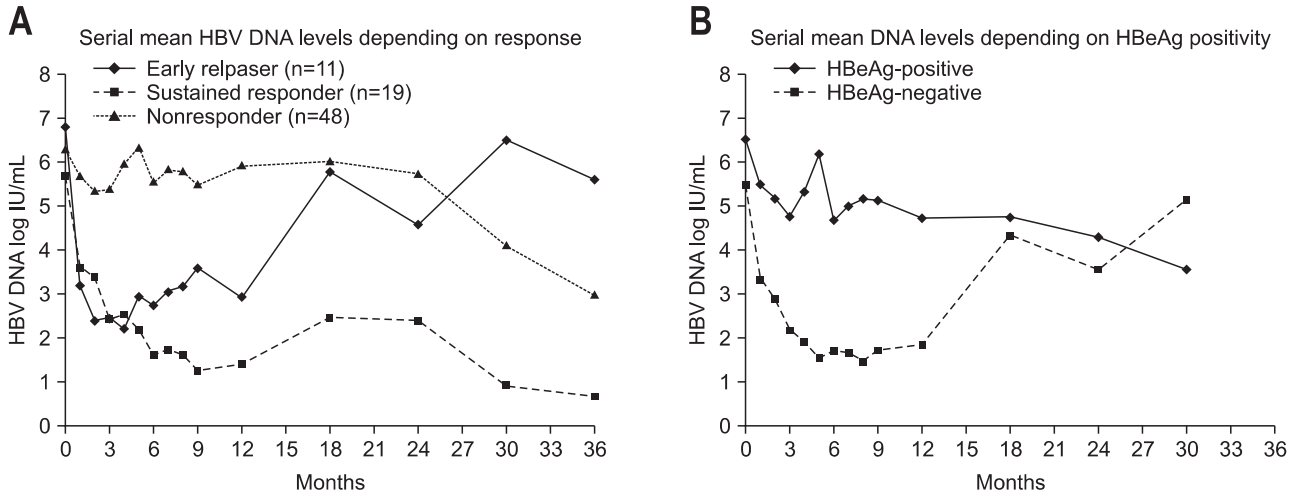

Fig. 2. (A) Serial changes in hepatitis B virus (HBV) DNA depending on viral response. (B) Serial changes in HBV DNA depending on hepatitis B e antigen (HBeAg) positivity.

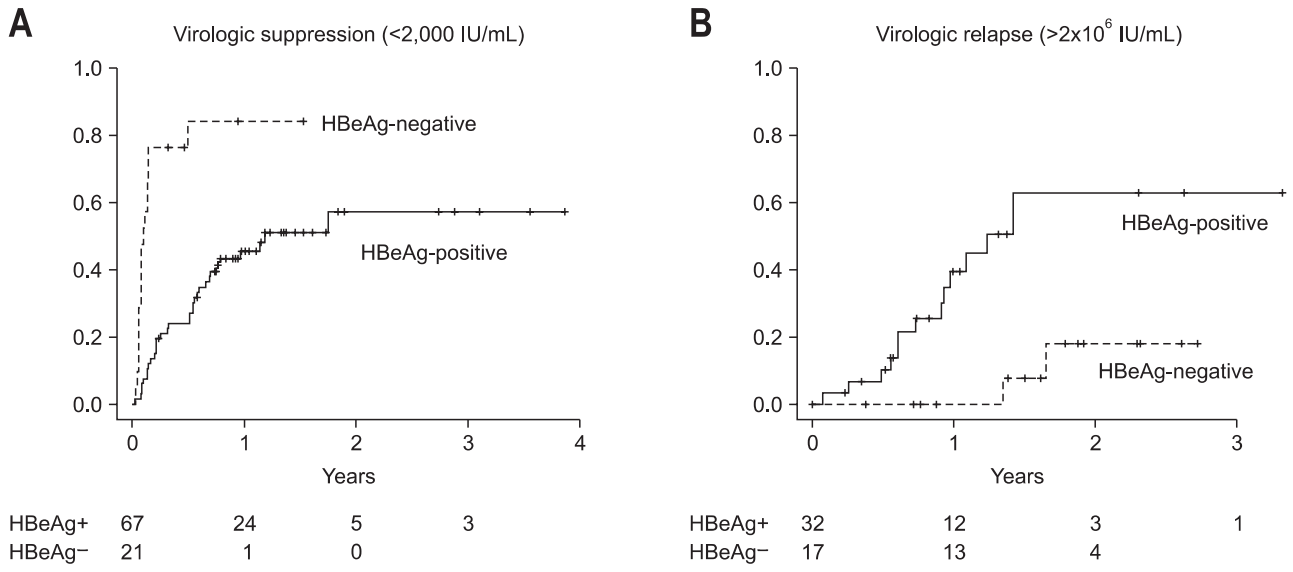

Fig. 3. (A) The rate of virologic suppression (<2,000 IU/mL). (B) The rate of virologic relapse (>2×10^6 IU/mL). Virologic response and relapse during the entire study period. (A) Time to suppression of hepatitis B virus (HBV) DNA to less than 2,000 IU/mL (p=0.000 by log rank test, hepatitis B e antigen [HBeAg]-positive vs HBeAg-negative). (B) Time to relapse of HBV DNA to more than 2×10^6 IU/mL after the suppression to less than 2,000 IU/mL (p=0.004 by log rank test, HBeAg-positive vs HBeAg-negative).

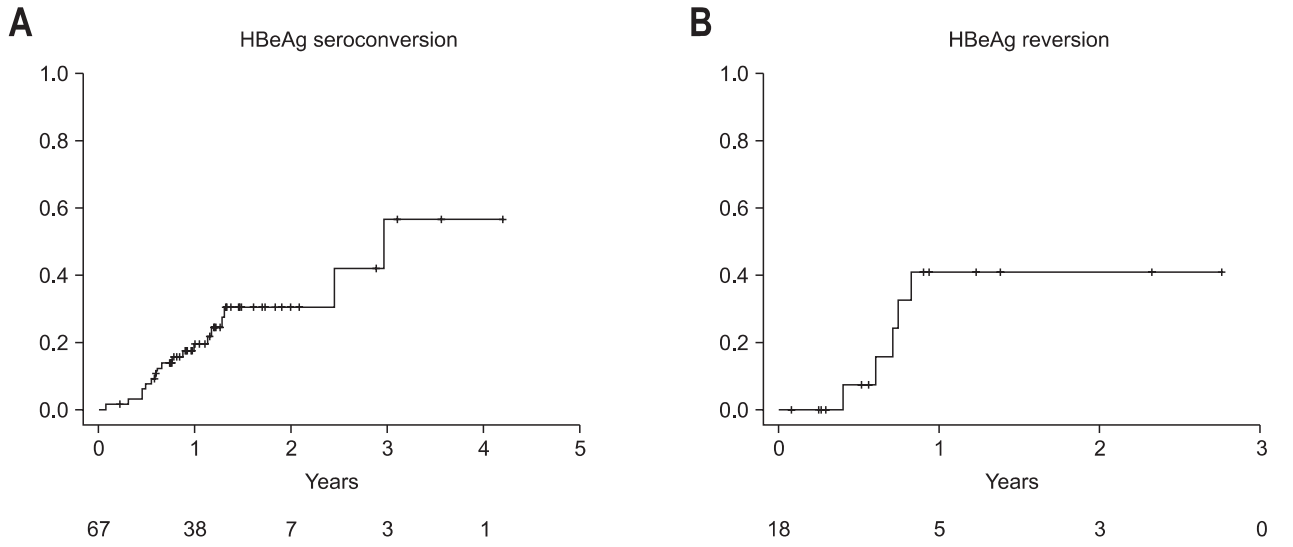

Fig. 4. (A) The rate of hepatitis B e antigen (HBeAg) conversion. (B) The rate of reversion of HBeAg. HBeAg conversion and reversion during the entire study period. (A) Time to HBeAg seroconversion to anti-HBe. (B) Time to reversion of HBeAg after seroconversion.

sion was 420 days (range, 29 to 1,535 days) (Fig. 4A). However, 27.8% (5/18) of HBeAg seroconverted patients reversed after 260 days (range, 147 to 300 days) HBeAg seroconversion (Fig. 4B).

All HBeAg-negative patients who achieved the sustained response maintained the virologic response without relapse during the whole follow-up period. For HBeAg-positive patients who achieved the sustained response, only one patient showed virologic breakthrough and HBeAg reversion 21 weeks after the sustained response. This patient had been treated with PEG-IFN α-2a for 24 weeks. Additional antiviral agents were prescribed to eighteen patients who failed treatment (n=12) or relapsed (n=6).

5. Safety results

The causes of premature discontinuation therapy depended on HBeAg positivity (Table 5). In the HBeAg-positive group, insufficient response was the main cause followed by adverse events and patient refusal to continue therapy. The principal cause of patient refusal was cost, although costs were partially met by health insurance. In the HBeAg-negative groups, adverse events were the main cause. The mean treatment period in the discontinuation group was 20.8±11.5 weeks. Twelve HBeAg-positive and eight HBeAg-negative patients developed adverse events

Table 5. Incidence of Discontinuation of Treatment and Adverse Events

During treatment	HBeAg-positive (n=67)	HBeAg-negative (n=21)	Total (n=88)
Total no. of discontinued patients	17 (25.3)	6 (28.6)	23 (26.1)
Treatment period, wk	21.2±13.2	19.7±4.1	20.8±11.5
Adverse events	4 (5.9)	3 (14.3)	7 (8.0)
Insufficient response	8 (11.9)	1 (4.7)	9 (10.2)
Others	5 (7.4)	2 (9.5)	7 (8.0)
Adverse events	12 (17.9)	8 (38.1)	20 (22.7)
General weakness	3	3	6
Flu-like symptoms	2	0	2
Edema	1	1	2
Drug eruption	0	1	1
Hair loss	1	0	1
Epigastric pain	0	2	2
Depression	2	0	2
Insomnia	1	0	1
Leukopenia	2	1	3

Data are presented as number (%) or mean±SD.
HBeAg, hepatitis B e antigen.

(Table 5). Symptomatic events in decreasing order were; general weakness, flu-like symptoms, epigastric pain, edema, depression, drug eruption, hair loss, and insomnia. Only three patients developed neutropenia. Of 20 patients, four HBeAg-positive and four HBeAg-negative patients ceased therapy prematurely due to general weakness, flu-like symptoms, drug eruption, epigastric pain, or neutropenia. There were no death or admission cases.

DISCUSSION

This study provides a valuable data on response to PEG-IFN α-2a treatment for CHB in Korean patients with genotype C in a clinical setting. Given the prevalence of the unfavorable C genotype and the high cost of PEG-IFN treatment could be less usage of PEG-IFN α-2a for CHB in Korea. Furthermore, unsatisfactory on-treatment response and adverse events cause the premature discontinuation of PEG-IFN α-2a treatment. Therefore, Korean doctors do not consider PEG-IFN α-2a as a first line treatment for CHB in real clinical practice, despite its being approved as a first line treatment in the West.[2,10]

In the present study, virologic response in HBeAg-negative group was acceptable but virologic and serologic response in HBeAg-positive group was relatively low as compared with previous studies. In a large study, which included 60% of Asian HBeAg-negative patients,[9] virologic responses (<2×10^4 copies/mL at the end of treatment and 24 weeks after treatment) were 81% and 43%, respectively. Rates of ALT normalization at the end of treatment and 24 weeks after treatment were 38% and 59% respectively. In the present study, the majority of HBeAg-negative patients achieved viral suppression to <2,000 IU/mL at the end of treatment and at 24 weeks after therapy completion, and the majority had a durable response. However, the undetectable rate of HBV DNA suppression by PEG-IFN α-2a was disappointing as compared with oral antiviral agents. The undetectable suppression rate at the end of treatment was 66.7% for HBeAg-negative patients, but fell to 30.8% at 24 weeks after treatment completion although ALT normalization was well maintained. This result is consistent with the finding that relapse after INF-α cessation is common in HBeAg-negative patients with sustained response rates of only 15% to 30%.[9,11-14] In contrast, during the whole follow-up period, only two HBeAg-negative patients developed the relapse of HBV DNA level >2×10^6 IU/mL. When we considered these results, PEG-IFN α-2a treatment in HBeAg-negative patients could suppress HBV DNA moderately as compared with oral agents and we recommend it as a first treatment for younger patients who want a definite treatment duration. In HBeAg-positive patients, virologic response and serologic response was less than that in Westerns.[5,8,15] In the present study, 23.8% of patients that completed therapy achieved the sustained response. Furthermore, most patients except one patient who achieved the sustained response, maintained this response for more than 2 years. These results compare well with published data of a 14% (<400 copies/mL) to 32% (<1×10^5 copies/mL) HBV DNA suppression rate at 24 weeks after treatment.[5,8,15] Although response to IFN in genotype C is known to be inferior to genotype A and B responses,[5,6] it was recently reported that genotype B and C infected patients with high ALT and low HBV DNA levels have a high likelihood of response to PEG-IFN.[1] In this previous report, the rate of combined HBV DNA <10^4 copies/mL and HBeAg loss/seroconversion varied from 19% to 32%. However, a number of HBeAg-positive patients in the present study discontinued therapy due to insufficient antiviral response, and this may have reduced practical virologic and serologic response rates as compared with previous controlled studies. Interestingly, only one relapsed HBeAg-positive patient who achieved the sustained response had been treated with 24 weeks of PEG-IFN. It was recently reported that shorter duration (24 weeks vs 48 weeks) PEG-IFN therapy is associated with inferior HBeAg seroconversion in HBV genotypes B or C (22.9% vs 36.2%).[16] Therefore, several guidelines[2,10,17] which recommend 90 to 180 μg/wk at least 6 months for HBeAg-positive patients and short term insurance coverage of Korea need to reflect these results.

In the present study, we investigated the serial HBV DNA levels to predict virologic response during treatment and follow-up. It is known that HBeAg-positive patients have lower end of treatment response and sustained response rates than HBeAg-

negative patients. However, the rate of early relapse in HBeAg-negative patients was higher than that in HBeAg-positive patients (18.2% vs 10.5%, p<0.05). These findings indicate that serial HBV DNA level should be carefully monitored even when HBeAg-negative patients achieve the end of treatment response. However, we were not able to identify the pattern or cut-off level of serial HBV DNA that predicted the early relapse. Both the early relapser and sustained responder showed similar HBV DNA reductions during the treatment period although HBV DNA levels at 6 months or later in the early relapser were higher than those in the sustained responder. These findings concurs with that low HBV DNA level at week 24 of treatment was associated with the sustained response in logistic analysis. Recently, it was reported that low levels of on-treatment HBsAg during therapy are associated with high rates of post-treatment response, including HBeAg seroconversion.[18] In addition, serial HBV DNA patterns in those with or without HBeAg seroconversion did not differ during the treatment period in HBeAg-positive patients (data not shown). Thus, serologic responses in HBeAg-positive patients might be affected by other immunologic factor, such as HBsAg titer and HBeAg titer, rather than by quantitative HBV DNA levels. Therefore, the effect of HBsAg titers on the sustained response and kinetics of HBsAg during PEG-IFN α-2a treatment period should be confirmed in a larger study.

In the present study, a number of patients prematurely discontinued treatment, which presents a barrier to the usage of PEG-IFN α-2a. Furthermore, the causes of discontinuation in the present study differed from identified in large controlled studies. In the present study, insufficient response (10.2%) and cost problem (4.5%) in addition to adverse events (9.1%) were cited as the main causes of discontinuation, whereas in large controlled studies have shown that only 3% to 7% and 1% to 3% of patients stopped treatment for safety or other reasons, respectively.[8,9] This discrepancy might be due to the retrospective, multicenter nature of the present study. The other limitations of this study are followed as. The antiviral response rate in per protocol analysis of the present study is similar to those found in controlled studies, but the high discontinuation rate due to insufficient antiviral response in the present study may have led to an inferior antiviral response in intention to treatment analysis to controlled studies. In addition, small number of patients during relative short period of follow-up in the present study was a limitation to identify predictors of sustained response in logistic analysis. This may also cause no responder of HBsAg even among sustained responder. However, patients who achieved the sustained response demonstrated a durable response (86.7% at 1 year after therapy completion). This result is consistent with that of a recent similar study conducted in Australia in a real clinical setting (60% at 2 years).[19] Furthermore, in this previous study, no definite predictor of sustained response other than a viral load of less than 6 log IU/mL at week 12 of therapy was identified in HBeAg-negative patients and no difference in HBV DNA dynamics during treatment was observed between patients who achieved sustained virologic responder or early relapser. However, in the present study, high baseline ALT level and good response at week 12 and 24 of therapy were associated with favorable factors for the end of treatment response and sustained response. Therefore it would appear that the patients who showed a favorable on-treatment response can be encouraged to persist with therapy and more identification of on-treatment predictors will be required.

Summarizing, the present study provides practical, real data obtained at several Korean institutes. The results obtained suggest that PEG-IFN α-2a therapy in Korean patients, in whom genotype C is predominant, achieves lower virologic response than in Westerns but favorable durability. However, the rate of premature discontinuation was found to be higher in the real clinical setting than in controlled trials. Therefore, we recommend that efforts should be made to identify pretreatment and on-treatment predictors of the sustained response, because these could be used to individualize therapy and maximize treatment outcomes.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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