Original Article

Pre-Treatment with Pegylated Interferon Alfa-2a Did Not Increase HBeAg Seroconversion in Chronic Hepatitis B, HBeAg-Positive Patients Treated with Entecavir

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ABSTRACT

Background: Treatment of chronic hepatitis B (CHB), HBeAg positive patients includes pegylated interferon (PegIFN) or nucleos(t)ide analogues (NUC). However, about two-thirds of patients treated with PegIFN do not achieve HBeAg seroconversion and may require treatment with NUC. So far, there are few data about outcomes of CHB patients treated with PegIFN followed by NUC. Whether pre-treatment with PegIFN offers more HBeAg seroconversion remains uncertain. The objective of this study was to investigate the outcome of patients pre-treated with PegIFN followed by entecavir compared with patients treated with entecavir alone.

Methods: This is a retrospective chart review from January 2005 to July 2012. There were 46 patients pre-treated with PegIFN alfa-2a for 48 weeks, who did not achieve HBeAg seroconversion and required treatment with entecavir (0.5mg) daily, compared with 50 patients treated with entecavir alone during the same period. HBeAg status and HBV DNA level at baseline and every 1 year after starting entecavir were collected and compared between the two groups.

Results: The PegIFN/entecavir group was younger (mean age 45.4 vs. 52.3 years, p=0.004) and had less advanced fibrosis/cirrhosis at baseline (8.9% vs. 35.4%, p=0.002) than in the entecavir group. Furthermore, the entecavir treatment duration was shorter in the PegIFN/entecavir group (116.8 vs. 162.5 weeks, p=0.004). After 1 year of entecavir treatment, there was no significant difference in the rates of HBeAg seroconversion, HBeAg loss, and undetectable HBV DNA in both groups (10.9% vs. 14.0%, p=0.643; 7.3% vs. 4.6%, p=0.669 and 54.3% vs. 64.0%, p=0.336; respectively). These outcomes were also not different between the two groups at year-2 through year-5 after entecavir treatment.

Conclusion: In HBeAg-positive CHB patients, pre-treatment with PegIFN alfa-2a before entecavir did not increase HBeAg seroconversion, HBeAg loss or HBV DNA suppression, when compared to patients treated with entecavir alone.

Key words : Pegylated interferon, PegIFN, chronic hepatitis B, entecavir

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Introduction

Chronic hepatitis B (CHB) is a major health problem worldwide especially in Asia. An estimate of 350 million persons worldwide is chronically infected with hepatitis B virus (HBV). CHB patients are at increased risk for developing cirrhosis, liver decompensation and hepatocellular carcinoma[1-2].

Currently, treatment of CHB consists of PegIFN or NUC, and the ultimate goal of CHB treatment is HBsAg seroconversion. However, the rate of HBsAg seroconversion in treated patients is not satisfactory[3-9]. Therefore, in HBeAg positive CHB patients, the goals of treatment are HBeAg seroconversion and viral suppression to decrease the risk of cirrhosis and cirrhotic complications[1]. With current standard treatment, however, the outcome is not yet satisfactory. Only one-third of patients achieve the treatment goal[1].

In patients treated with PegIFN, about two-thirds do not achieve HBeAg seroconversion and many need therapy with NUC after PegIFN treatment. So far, there are few data about the outcomes of CHB patients treated with PegIFN followed by NUC to indicate whether or not such pre-treatment with PegIFN will offer more HBeAg seroconversion or viral suppression. In Liang Xuesong, et al. study[11], in patients who did not achieve treatment goal after PegIFN treatment, it was found that patients who received sequential telbivudine after PegIFN showed more HBeAg seroconversion and more HBV DNA suppression than those who received adefovir add-on with PegIFN. The main limitation of this study was the small numbers of cases and comparison between different NUCs.

Our study was aimed to investigate the outcome of HBeAg positive CHB patients pre-treated with PegIFN followed by entecavir, compared with patients treated with entecavir alone.

Material and methods

Study design and population

This was a retrospective chart review from January 2005 to July 2012, of patients with CHB who received treatment at Siriraj Hospital, Bangkok, Thailand, with HBeAg positivity at the time of entecavir initiation. Patients aged 18 years or over who received entecavir for at least 1 year were selected. In the pegIFN/ETV group, patients had received pegylated interferon alfa-2a (PegIFN-2a) for at least 24 weeks and the interval between the last dose of PegIFN-2a and entecavir initiation was not more than 1 year. In the entecavir group, patients had received only entecavir right from the beginning. Patients were excluded if they had hepatitis C or HIV co-infection, diagnosis of decompensated cirrhosis (Child-Pugh score B-C) before starting PegIFN treatment, or had previously received any NUC before starting.

Patients' demographic data including age, sex, body mass index, co-morbid disease(s), risk factor of HBV infection, history of alcohol use, duration of HBV infection, duration of HBV treatment, and evidence of cirrhosis or advanced fibrosis (by ultrasonography, Fibroscan® or liver biopsy) were collected. Laboratory data including baseline HBV DNA level (IU/mL), baseline alanine aminotransferase (ALT) and viral markers (HBeAg, anti-HBe, HBsAg, anti-HBs) at the start of treatment and at years 2 to 5 after treatment were also collected. This study was approved by the Ethic Committee of Siriraj Hospital.

Outcomes measurement

The primary outcome was to compare the between two groups rate of HBeAg seroconversion and the rate of undetectable HBV DNA at 1 year after starting entecavir. The secondary outcome was to compare the rate of HBeAg seroconversion, undetectable HBV DNA and complication of CHB at year 2 to 5 after treatment with entecavir.

Statistical analysis

Descriptive statistics were reported using mean, standard deviation, median, minimum, maximum and percent as appropriate. Chi-square test or Fisher's exact test was used for categorical variable whereas independent *t*-test or Mann-Whitney *U* tests were used for continuous variable. The rates of HBeAg seroconversion and undetectable HBV DNA in both groups were compared with independent *t*-test or Mann-Whitney *U* test as appropriate. *P*-value of <0.05 was considered statistical significance. Statistical data analysis was performed using SPSS version 13.

Results

There were 96 patients, 46 in the PegIFN/

entecavir group and 50 in the entecavir alone group. Patients in the PegIFN/entecavir group were younger (mean age 45.4 vs. 52.3 years, p=0.004) and had less advanced fibrosis/cirrhosis at baseline (8.9% vs. 35.4%, p=0.002). The entecavir treatment duration was shorter in the PegIFN/entecavir group (116.8 vs. 162.5 weeks, p=0.004). The initial HBV DNA level and ALT level before starting entecavir were not significantly different between the two groups (Table 1).

After 1 year of entecavir treatment, there was no significant difference in the rate of HBeAg seroconversion (10.9% vs. 14.0%, p=0.643), HBeAg loss (7.3% vs. 4.6%, p=0.669) and undetectable HBV DNA in both groups (54.3% vs. 64.0%, p=0.336). These outcomes were also not different at year-2 through year-5 after entecavir treatment (Table 2). One patient in the entecavir only group had HBsAg seroconversion after 3 years of entecavir treatment, but no HBsAg seroconversion or HBsAg loss was found in patients in the PegIFN/entecavir group. No significant difference in the rate of CHB complication (new cirrhosis or HCC) between the two groups was noted

Table 1. Baseline characteristics of the two treatment groups.

	Number (%) or Mean ± SD		*p*-value
	PegIFN/ETV (n=46)	**ETV (n=50)**	
Sex: Male, n (%)	25 (54.3%)	24 (48.0%)	0.534
Age (yrs.), mean ± SD	45.4 ± 10.0	52.3 ± 12.6	0.004
Body mass index (kg/m^2)	22.5 ± 3.5 (n=41)	24.0 ± 4.2 (n=47)	0.058
Underlying disease			0.480
DM	2 (4.3%)	2 (4.0%)	
Cardiovascular disease	7 (15.2%)	11 (22.0%)	
Autoimmune disease (SLE)	0	1 (2.0%)	
Fatty liver	0	2 (4%)	
Other (CA breast)	0	1 (2%)	
Risk factor for HBV infection			0.832
Family history of CHB	10 (30.3%)	13 (26.5%)	
Tattooing	0	1 (2.0%)	
Unsafe sex	1 (3.0%)	1 (2.0%)	
History of alcohol used (more than 20 g/d, 10 yrs.)	6 (19.4%)	8 (16.7%)	0.901
Evidence of cirrhosis or advance fibrosis when starting treatment	4 (8.9%)	17 (35.4%)	0.002
Duration of HBV infection (yrs.)	10 (2, 25)	5 (1, 35)	0.069
Duration of ETV treatment (wks.)	116.8 ± 70.3	162.5 ± 78.7	0.004
Initial HBV DNA (IU/mL)			
- 2,000 - 19,999	3 (6.5.%)	1 (2.0%)	0.77
- 20,000 - <200,000	3 (6.5%)	2 (4.0%)	
- 200,000 - <2,000,000	7 (15.3%)	17 (34.0%)	
- 2,000,000 - <170,000,000	23 (50%)	18 (36.0%)	
- ≥170,000,000	10 (21.7%)	12 (24.0%)	
Initial ALT level (U/L)			
- <40	9 (19.6%)	16 (32.0%)	0.467
- 40 - 79	18 (39.1%)	16 (32.0%)	
- 80 - 200	14 (30.4%)	11 (22.0%)	
- > 200	5 (10.9%)	7 (14.0%)	

Table 2. Results in the two groups after treatment with entecavir (number of total patient per year in PegIFN/ETV group / ETV alone group).

	PegIFN/ETV	ETV	*p*-value
HBeAg seroconversion			
- 1st year (n = 46/50)	5 (10.9)	7 (14.0)	0.643
- 2nd year (n = 26/35)	3 (11.5%)	11 (31.4)	0.068
- 3rd year (n = 15/27)	3 (20.0%)	6 (22.2%)	1.000
- 4th year (n = 9/17)	3 (33.3%)	3 (17.6%)	0.628
- 5th year (n = 3/6)	1 (33.3%)	1 (16.7%)	1.000
- 6th year (n = 0/1)	0	1	
HBeAg loss			
- 1st year (n = 41/43)	3 (7.3%)	2 (4.6%)	0.669
- 2nd year (n = 23/24)	4 (17.4%)	1 (4.1%)	0.180
- 3rd year (n = 12/21)	4 (33.3%)	2 (9.5%)	1.590
- 4th year (n = 6/14)	3 (50.0%)	2 (14.3%)	1.310
- 5th year (n = 2/5)	1 (50.0%)	0	0.286
- 6th year (n = 0/1)	0	1	
HBeAg seroconversion or loss			
- 1st year (n = 46/50)	8 (17.4%)	9 (18.0%)	0.938
- 2nd year (n = 26/35)	7 (26.9%)	12 (34.3%)	0.539
- 3rd year (n = 15/27)	7 (46.7%)	8 (29.6%)	0.270
- 4th year (n = 9/17)	6 (66.7%)	5 (29.45)	0.103
- 5th year (n = 3/6)	2 (66.7%)	1 (16.7%)	0.226
- 6th year (n = 0/1)	0	1	
HBV DNA undetectable			
- 1st year (n = 46/50)	25 (54.3%)	32 (64.0%)	0.336
- 2nd year (n = 27/37)	21 (77.8%)	30 (81.1%)	0.746
- 3rd year (n = 16/28)	15 (93.8%)	25 (89.3%)	1.000
- 4th year (n = 9/18)	9 (100%)	16 (88.9%)	0.538
- 5th year (n = 3/9)	3 (100%)	9 (100%)	
- 6th year (n=0/1)	0	1 (100%)	
New complication (Cirrhosis or HCC)	1 (2.2%)	3 (6.0%)	0.618

after 5 years of follow-up (2.2% vs. 6.0%, p= 0.618).

Discussion

The majority of CHB patients treated with PegIFN did not achieve treatment goal and required NUC treatment after stopping PegIFN. To our knowledge, there were few data about the outcome of such patients. In Wong V W, et al. study[10], the rate of HBeAg seroconversion in HBeAg positive CHB patients progressively increased after stopping PegIFN treatment. Among patients who remained HBeAg positive at the end of PegIFN treatment, 69% developed HBeAg seroconversion during 5-year follow up. This study suggested that PegIFN may have immunomodulatory effect on HBeAg seroconversion long after the end of treatment. But there was no control group to compare the rate of HBeAg seroconversion.

In Liang Xuesong, et al. study[11], the authors compared the outcome of HBeAg positive CHB patient treated with PegIFN who did not achieve treatment goal, follow by telbivudine or add-on adefovir with PegIFN. The sequential telbivudine group showed higher HBeAg seroconversion rate and undetectable

HBV DNA at 48 weeks after starting telbivudine. However, from this study, they compared between different kind of sequential treatment (telbivudine alone or add-on adefovir), different NUCs and small number (11 and 13 patients in two groups).

Our study was designed to assess the efficacy of Peg-IFN pre-treatment followed by entecavir compared with entecavir alone. The outcomes showed no significant difference between the two groups in HBeAg seroconversion rate or undetectable HBV DNA at 1 year after starting entecavir. The duration of entecavir treatment in the PegIFN/entecavir group was shorter than in the entecavir group, as patients in the first group had PegIFN for about one year. Although the study from Hong Kong[10] showed that PegIFN increased long term HBeAg seroconversion, our study when compared with entecavir, there was no significantly difference in rate of HBeAg seroconversion and undetectable HBV DNA when followed to 5 years. Thus, in HBeAg positive, CHB patients, sequential PegIFN/entecavir treatment did not lead to a better outcome than entecavir only. However, patients who received sequential PegIFN/entecavir were those who did not achieve HBeAg seroconversion after PegIFN treatment. Such patients may represent a hard-to-treat group who still response to entecavir treatment no less than those who received entecavir from the beginning. There was difference in baseline histology, with more advanced histology in the entecavir group, but there were no differences in baseline ALT and HBV DNA between the groups.

We did not compare the rate of HBsAg seroconversion the complication of CHB (cirrhosis or HCC) due to small numbers. Further study with larger numbers and longer follow up periods would provide more information about these outcomes.

Conclusion

In HBeAg-positive CHB patients, pre-treatment with PegIFN alfa-2a before entecavir did not appear to increase HBeAg seroconversion, HBeAg loss or HBV DNA suppression, when compared with patients treated with entecavir only.

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