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 >2×10^6 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. In trials in Asian patients with hepatitis B e antigen (HBeAg)-negative 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. Genotype C is the principal type of HBV in Koreans and is known to be associated with lower rates of HBeAg seroconversion than genotype A or B. 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. The findings of several well-controlled
large scale trials suggest that PEG-IFN α-2a is both effective and safe for the treatment of CHB, 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. 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 $2 \times 10^6$ to $2 \times 10^8$ 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, 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. 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.](image-url)