Research Article

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Kinetics of hepatitis B surface antigen differ between treatment with peginterferon and entecavir

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Background & Aims: We aimed to investigate serum hepatitis B surface antigen (HBsAg) levels in patients with chronic hepatitis B virus (HBV) infection during peginterferon (PEG-IFN) and entecavir (ETV) monotherapy.

Methods: HBsAg was quantified (Abbott ARCHITECT) at baseline and during antiviral therapy (weeks 12, 24, 36, 48) in hepatitis B e antigen (HBeAg-) positive patients treated with ETV ($n = 33$) or PEG-IFN ($n = 61$) and in HBeAg-negative patients treated with ETV ($n = 37$) or PEG-IFN ($n = 69$).

Results: Within the HBeAg-positive population, patients treated with PEG-IFN tended to have a steeper HBsAg decline than ETV-treated patients (mean decline 0.94 versus 0.38 log IU/ml at week 48, $p = 0.07$ for comparison of the slope of HBsAg decline). The HBsAg decline was larger in those patients who became HBeAg negative, irrespective of the treatment regimen. A decline in HBsAg was confined to ETV-treated patients with elevated baseline alanine aminotransferase (ALT) levels, whereas HBsAg decline was not associated with baseline ALT in patients treated with PEG-IFN. Within the HBeAg-negative population, PEG-IFN induced a significant HBsAg decline, while HBsAg did not decrease in ETV-treated patients (0.56 versus −0.10 log IU/ml, $p < 0.001$). Both in HBeAg-positive and HBeAg-negative patients, the decline in serum HBV DNA was larger in patients who received ETV as compared to patients treated with PEG-IFN.

Conclusions: In HBeAg-positive patients, the decline in serum HBsAg is mainly confined to patients who clear HBeAg, by either PEG-IFN or ETV treatment. In HBeAg-negative patients, PEG-IFN therapy resulted in a significant reduction in HBsAg levels, whereas HBsAg did not decrease in ETV-treated patients.

Introduction

Chronic hepatitis B (CHB) can be controlled in most patients with the currently available treatment options, but complete eradication of the hepatitis B virus (HBV) is rarely achieved. HBV covalently closed circular DNA (cccDNA) plays a major role in viral persistence and its clearance is thought to be the limiting factor in eliminating the infection [1]. Previous studies demonstrated that both (pegylated) interferon (IFN) and nucleos(t)ide analogue (NA) therapies result in a reduction of intrahepatic cccDNA [2–4]. In addition, intrahepatic cccDNA was shown to be a strong predictor of sustained off-treatment virological response [5]. Serum hepatitis B surface antigen (HBsAg) levels are known to reflect cccDNA in the liver, and a reduction of HBsAg levels correlates well with that of cccDNA [2–4].

HBsAg clearance from serum approximates clinical cure and is associated with improved survival [6]. The kinetics of HBsAg decline have recently been described in patients treated with standard IFN, PEG-IFN, lamivudine (LAM), and adefovir (ADV) monotherapy [2,7,8]. It was demonstrated that the measurement of serum HBsAg concentration during therapy may allow for the identification of sustained responders to PEG-IFN more reliably than serum HBV DNA [9]. However, the effect of potent NA such as entecavir (ETV) and tenofovir (TDF) on serum HBsAg levels is unknown. Furthermore, the efficacy of PEG-IFN in terms of HBsAg decline was only compared to inferior oral agents such as LAM and ADV.

The aim of our study was (i) to assess on-treatment serum HBsAg kinetics in hepatitis B e antigen (HBeAg-)positive and HBeAg-negative CHB patients treated with PEG-IFN or ETV monotherapy, (ii) to compare the efficacy of PEG-IFN and ETV monotherapy in terms of HBsAg decline, and (iii) to identify baseline factors associated with HBsAg decline, after 48 weeks of antiviral therapy.

Keywords: Peginterferon; Entecavir, Hepatitis B; Quantitative HBsAg.
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Abbreviations: CHB, chronic hepatitis B; HBV, hepatitis B virus; cccDNA, covalently closed circular DNA; IFN, interferon; NA, nucleos(t)ide analogue; HBsAg, hepatitis B surface antigen; LAM, lamivudine; ADV, adefovir; ETV, entecavir; TDF, tenofovir; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; ULN, upper limit of the normal range; anti-HBe, antibody against HBeAg; PCR, polymerase chain reaction.

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Patients and methods

Study population

We studied all consecutive HBV-monoinfected patients treated with ETV monotherapy for at least 48 weeks between January 2005 and May 2008 at the Erasmus MC University Medical Center Rotterdam. Patients treated with PEG-IFN monotherapy were derived from two randomized controlled trials (total treatment duration 48 and 52 weeks) [10,11]. The studies conformed to the ethical guidelines of the Declaration of Helsinki. Informed consent was obtained from all patients.

Laboratory tests

Patients attended the outpatient clinic at least every 12 weeks for routine examinations and laboratory assessments. Serum alanine aminotransferase (ALT) levels were measured using automated techniques and are expressed as values representing a ratio to the upper limit of the normal range (ULN). Determination of HBeAg and antibody against HBeAg (anti-HBe) status was performed using commercially available enzyme immunoassays. Serum HBsAg was quantified at baseline and during antiviral therapy (weeks 12, 24, 36 and 48) using the ARCHITECT HBsAg assay (Abbott laboratories; range 0.05–250 IU/ml). Serum HBV DNA levels were measured using commercial TaqMan polymerase chain reaction (PCR) assays (Roche Molecular Systems; lower limit of detection 70 copies/ml), except for the HBeAg-positive patients treated with PEG-IFN for whom an in-house-developed TaqMan PCR assay based on the EuroHep standard was used (lower limit of detection 400 copies/ml) [12]. It has previously been demonstrated that there is an excellent correlation between these assays [13].

Statistical analysis

Group-matching between the ETV and PEG-IFN groups was performed by their baseline HBV DNA concentration and aimed at a 2:1 ratio in order to increase power, as described by Pocock [14]. Baseline HBV DNA was selected, because this factor was previously found to be associated with the degree of HBsAg decline during PEG-IFN therapy [7].

Serum HBsAg and HBV DNA levels were logarithmically transformed for analysis. Continuous variables are presented as mean (standard deviation) or median (interquartile range), where appropriate. The lower limit of detection of 400 copies/ml of the in-house PCR assay was applied to all HBV DNA results to allow comparison between the treatment groups. Continuous variables were compared using the *t*-test or the Mann–Whitney test. Categorical variables were compared using the Chi-square or Fisher's exact test. The association between baseline factors and the degree of HBsAg decline was assessed by linear regression analyses applying mixed modelling techniques with a random intercept and a random slope per subject, and with a covariance structure depending on the treatment regimen. Statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) and the SAS 9.2 program (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided and were evaluated at the 0.05 level of significance.

Results

Baseline characteristics

A total of 200 HBV-infected patients were included in the study. The HBeAg-positive population consisted of 61 patients treated with PEG-IFN and 33 patients treated with ETV. The HBeAg-negative population consisted of 69 patients treated with PEG-IFN and 37 ETV-treated patients (Fig. 1). Baseline characteristics are presented in Table 1. HBeAg-positive patients treated with PEG-IFN and ETV were comparable at baseline except for serum ALT level, distribution of HBV genotypes, and prevalence of liver cirrhosis (Table 1). Within the HBeAg-negative population, the treatment groups were balanced except for ethnicity, distribution of HBV genotypes, and prevalence of liver cirrhosis (Table 1).

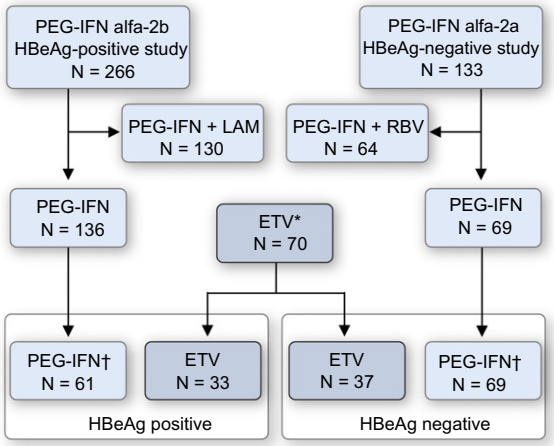

Fig. 1. Study profile. *All consecutive patients treated with ETV monotherapy for at least 48 weeks were included; †Patients treated with PEG-IFN monotherapy were randomly selected from two randomized controlled trials [10,11], the PEG-IFN and ETV groups were group-matched according to their baseline HBV DNA level. RBV: ribavirin.

HBeAg-positive patients tended to be younger (38 versus 41 years, $p = 0.10$) and had higher baseline serum HBV DNA and HBsAg levels compared with HBeAg-negative patients (8.4 versus 6.8 log copies/ml for HBV DNA and 4.2 versus 3.8 log IU/ml for HBsAg, $p < 0.001$ for both comparisons), while median ALT levels were similar (2.3 versus 2.5 ULN, $p = 0.42$).

Baseline serum HBsAg and HBV DNA levels showed a significant positive correlation in HBeAg-positive patients ($R = 0.54$, $p < 0.001$), while HBsAg and HBV DNA were not correlated in HBeAg-negative patients ($R = 0.09$, $p = 0.36$).

HBeAg-positive patients

Virological and biochemical response rates

Within the HBeAg-positive population, PEG-IFN therapy resulted in a higher rate of HBeAg clearance at week 48 compared to ETV [21 (34%) versus 3 (9%) patients, $p = 0.007$; Table 2]. HBsAg loss (HBsAg <0.05 IU/ml) occurred in 6 (10%) patients in the PEG-IFN group, but was not achieved in patients treated with ETV ($p = 0.09$; Table 2). In contrast, the proportion of patients with HBV DNA <400 copies/ml at week 48 was higher in the ETV group [17 (52%) versus 10 (16%) patients in the ETV and PEG-IFN group, respectively; $p < 0.001$; Table 2].

On-treatment HBsAg and HBV DNA decline

The decline in serum HBsAg, during 48 weeks of monotherapy with PEG-IFN and ETV in HBeAg-positive patients, is displayed in Fig. 2A. HBsAg decreased significantly during PEG-IFN therapy (mean decline 0.94 log IU/ml at week 48, $p < 0.001$) and to a lesser extent in ETV-treated patients (0.38 log IU/ml, $p = 0.07$). The difference in HBsAg decline was not significant between these two groups ($p = 0.15$). Fig. 2B shows the decline in serum HBV DNA for the two treatment groups. HBV DNA levels decreased significantly during PEG-IFN and ETV therapy ($p < 0.001$ compared to baseline in both groups). In contrast to HBsAg, the suppression of HBV DNA was stronger in the ETV-treated patients (mean