Short communication

Pegylated interferon results in higher serological, but not virological, response rates when compared to continuous entecavir

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Background: Hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) clearance are associated with an improved prognosis in chronic hepatitis B (CHB) patients. These end points are more often achieved with a one-year course of pegylated interferon (PEG-IFN) compared with one year of nucleoside/nucleotide analogue therapy. However, prolonged nucleoside/nucleotide analogue therapy may result in comparable serological response rates as with PEG-IFN.

Methods: We compared serological and virological response rates among HBeAg-positive CHB patients treated with long-term continuous entecavir (ETV; n=91) for a median of 92 (IQR 50–132) weeks or one year of PEG-IFN (n=266) with comparable follow-up.

Results: Median follow-up was 92 weeks (IQR 78–198) for patients treated with PEG-IFN and 92 weeks (IQR 50–132) for patients treated with ETV. Finite PEG-IFN therapy resulted in significantly higher rates of HBeAg seroconversion (adjusted hazard ratio [HR] 3.16; P<0.001) and HBsAg clearance (HR 5.66; P=0.027) when compared to prolonged ETV treatment, whereas, ETV resulted in higher rates of HBV DNA undetectability (OR 31.14; P<0.001) also after adjustment for HBV genotype and other relevant baseline factors.

Conclusions: Our study shows that finite PEG-IFN is associated with a higher probability of serological, but not virological, response for HBeAg-positive CHB patients when compared to prolonged ETV, even after correction for baseline differences.

Introduction

Prolonged infection with the HBV may ultimately result in severe liver-related morbidity and mortality, and treatment of chronic hepatitis B (CHB) is therefore indicated in patients with persistent liver inflammation [1–3]. Hepatitis B e antigen (HBeAg) seroconversion (HBeAg clearance with positive anti-HBe) and hepatitis B surface antigen (HBsAg) seroclearance are important treatment end points in HBeAg-positive (CHB) [1] because they are associated with disease remission, a reduced risk of hepatocellular carcinoma and an improved prognosis [4–6]. These serological end points are more often achieved with a one-year course of pegylated interferon (PEG-IFN) when compared to one year of nucleoside/nucleotide analogues (NA), however, prolonged NA therapy may result in serological response rates approximating those achieved with PEG-IFN [7,8]. However, head-to-head comparisons of finite PEG-IFN versus long-term NA therapy have not been performed and differences in baseline characteristics prohibit direct comparison of previously published study results. We therefore aimed to compare rates of HBeAg seroconversion and HBsAg clearance, as well as HBV DNA undetectability, in HBeAg-positive CHB patients treated with continuous entecavir (ETV) monotherapy or one year of PEG-IFN with subsequent off-treatment follow-up.

Methods

Patients and follow-up

A total of 266 HBeAg-positive CHB patients were treated with PEG-IFN-α2b (PegIntron, Schering–Plough, Kenilworth, NJ, USA) for 52 weeks ± lamivudine (LAM; Zefix, GlaxoSmithKline, Greenford, UK) [8]. Patients were subsequently followed-up for another 6 months off-treatment and were enrolled in a long-term follow-up study [9]. Key inclusion criteria for this study were: HBsAg-positive for at least 6 months
before randomization, HBeAg-positivity, elevated serum alanine aminotransferase (ALT) levels <10× the upper limit of normal (ULN), and serum HBV DNA of more than 1.0×10⁵ copies/ml. Another 91 consecutive NA-naive patients were treated with ETV 0.5 mg daily as recommended by current treatment guidelines and were followed-up at the outpatient clinic at least every 3–6 months. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice.

Laboratory assays
(Anti-)HBeAg and HBsAg tests were performed using commercially available ELISA kits. HBV DNA was measured at baseline using real-time Taqman-based methods [8]. ALT was measured locally and was expressed as multiples of the ULN. HBV genotype was assessed by line-probe assay (Innogenetics, Ghent, Belgium).

Statistical analyses
HBeAg seroconversion (HBeAg negativity with anti-HBe) and HBsAg clearance rates were compared by Kaplan–Meier and Cox-proportional hazard analyses. Rates of HBV DNA undetectability were evaluated at week 78 (that is, 6 months post-treatment for patients treated with PEG-IFN) and at last follow-up evaluation. The analysis at last follow-up was limited to patients treated with ETV for ≥78 weeks. Follow-up time was calculated from start of treatment, and is expressed as median with the IQR. Follow-up was terminated in patients retreated after PEG-IFN and serological status before retreatment used as outcome parameter. SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) and the SAS 9.2 program (SAS Institute Inc., Cary, NC, USA) were used to perform statistical analyses. All statistical tests were two-sided and were evaluated at the 0.05 level of significance.

Results
Study cohort
Treatment outcomes did not differ between patients treated with PEG-IFN ±LAM, and patients were therefore pooled for this analysis [8,9]. Median follow-up was 92 weeks (IQR 78–198) for patients treated with PEG-IFN, and 92 weeks (IQR 50–132) for patients treated with ETV (P<0.001). A total of 323, 271, 166 and 109 patients were still in follow-up at weeks 48, 78, 96 and 144, respectively. HBV genotype distributions among patients treated with PEG-IFN were A/B/C/D/other in 34%, 9%, 15%, 39% and 4%, compared to 27%, 8%, 21%, 33% and 11% in the ETV group (P=0.11). The PEG-IFN and ETV groups were also well-balanced with regard to age (34.95 versus 36.93 years; P=0.21), sex (78% male versus 75%; P=0.35) and previous IFN therapy (both 21%; P=0.97). Baseline HBV DNA levels were higher in patients treated with PEG-IFN (9.06 versus 7.98 log copies/ml; P<0.001) as were ALT levels (4.30 versus 3.05 times the ULN; P=0.004).

HBeAg seroconversion
A total of 114 (32%) patients achieved HBeAg seroconversion in a median of 78 weeks (IQR 52–120). By Kaplan–Meier analysis, the cumulative probability of HBeAg seroconversion was higher in patients treated with PEG-IFN for one year versus those treated with long-term ETV (P=0.007). PEG-IFN therapy remained an independent determinant of HBeAg seroconversion in a Cox proportional hazard model; the hazard ratio (HR) for PEG-IFN versus ETV was 3.16 (95% CI 1.64, 6.75; P<0.001), after adjustment for HBV genotype, baseline ALT and baseline HBV DNA (Figure 1A).

HBsAg loss
A total of 30 (8%) patients cleared HBsAg in 92 weeks (IQR 78–170). By Kaplan–Meier analysis, cumulative HBsAg clearance rates were higher in patients receiving PEG-IFN therapy compared to patients treated with ETV (P=0.032). In a Cox proportional hazards model, PEG-IFN therapy was independently associated with HBsAg clearance, with an HR of 5.66 (95% CI 1.17, 101.80; P=0.027) after adjustment for HBV genotype, age and previous IFN exposure (Figure 1B).

HBV DNA undetectability
At week 78, a total of 69 (21% of total cohort) patients had undetectable HBV DNA. HBV DNA undetectability was achieved in 77% of ETV treated patients, compared to only 8% of patients treated with PEG-IFN (P<0.001). At last follow-up evaluation, 90 (39%) patients achieved undetectable HBV DNA, comprising 92% of patients on ETV, and 19% of PEG-IFN treated patients (P<0.001). In a logistic regression model, ETV therapy (OR 31.14, 95% CI 13.30, 72.90; P<0.001), HBV genotype A (OR 3.54, 95% CI 1.58, 7.95; P=0.002) and log HBV DNA (OR 0.65, 95% CI 0.48, 0.89; P=0.007) but not ALT (P=0.74) were independently associated with HBV DNA undetectability at week 78. An interaction term of HBV genotype and therapy was non-significant (P=0.26).

Discussion
This retrospective cohort study compared a finite course of PEG-IFN to prolonged potent NA therapy for serological and virological response rates. We found that PEG-IFN results in higher rates of HBeAg seroconversion and HBsAg seroclearance than continuous ETV therapy, and this difference remained after adjustment for important baseline factors. Nevertheless, HBV
DNA undetectability was achieved in only a minority of PEG-IFN treated patients, whereas most patients on ETV achieved this end point.

PEG-IFN and the NA have distinctly different modes of action in CHB [10]. PEG-IFN is an immunomodulator with limited direct antiviral efficacy that is able to induce a host immune response in a subset of patients [11]. NA competitively inhibits HBV polymerases and thus HBV DNA production. Several studies have shown that currently approved potent NA ETV and TDF can induce and maintain undetectable HBV DNA levels for prolonged therapy duration with a low risk of viral resistance or complications [7,12]. However, relapse is common after discontinuation [13]. HBeAg seroconversion has previously been shown to be associated with an improved prognosis [4–6] and is considered a first step towards immune control over HBV. The current study shows that this end point is more often achieved with a finite course of PEG-IFN than with prolonged ETV therapy, suggesting that immune control can more often be achieved with PEG-IFN. However, long-term follow-up studies of patients treated with PEG-IFN have revealed that some patients maintain elevated HBV DNA levels after HBeAg seroconversion [9,14]. Similarly, in patients treated with NA, viral rebound is frequently observed when therapy is discontinued after HBeAg seroconversion [15].

Our study also shows that a finite course of PEG-IFN results in superior rates of HBsAg seroclearance, the closest outcome to clinical cure one can hope to achieve in CHB [16,17]. HBsAg clearance is durable, confers an excellent long-term prognosis and is associated with a low probability of HBV reactivation in immune competent patients [4,18]. Although HBsAg clearance is only rarely achieved with currently available agents, particularly in patients treated with NA, we showed that a reasonable proportion of patients treated with PEG-IFN may achieve this end point during treatment and long-term off-treatment follow-up. This is in line with recent studies showing increased decline of HBsAg levels in patients treated with PEG-IFN, when compared to patients treated with ETV [19–21].

Despite the serological responses, persistence of HBV DNA after PEG-IFN is a reality in the majority of patients [9,14]. In contrast, nearly all patients on ETV achieved HBV DNA undetectability, and thus disease remission, while on-treatment. Taking into consideration the considerable side effects of PEG-IFN and the limited response rates, PEG-IFN therapy should be limited to those patients with the highest chances of achieving both serological and virological response, whereas ETV is a powerful treatment option for the vast majority of patients.

Although the current study was not randomized, we conducted a thorough multivariate analysis including all major determinants of serological response [22]. Of note, the HBV genotype distribution was comparable in the two cohorts, and we adjusted for baseline ALT and HBV DNA levels, age, sex, presence of cirrhosis and previous IFN exposure when necessary. A second limitation of
is that we pooled patients treated with PEG-IFN ± LAM to increase power. Importantly, several independent randomized studies and a meta-analysis have revealed no benefits of combination therapy [8,13,14,22].

In conclusion, our study shows that a finite course of one-year PEG-IFN results in superior rates of HBeAg seroconversion and HBsAg seroclearance, but not HBV DNA undetectability, when compared to prolonged ETV monotherapy.

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References