Original article

Durable hepatitis B surface antigen decline in hepatitis B e antigen-positive chronic hepatitis B patients treated with pegylated interferon-α2b: relation to response and HBV genotype

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Background: On-treatment decline of serum hepatitis B surface antigen (HBsAg) may reflect the immunomodulatory effect of pegylated interferon (PEG-IFN) for hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB). We compared HBsAg decline across HBV genotypes between combined responders (HBeAg loss and HBV DNA < 10,000 copies/ml at week 78), HBeAg responders (HBeAg loss with HBV DNA > 10,000 copies/ml) and non-responders. Methods: HBsAg was measured at baseline, on-treatment and 6 months post-treatment in 221 HBeAg-positive CHB patients treated with PEG-IFN with or without lamivudine for 52 weeks, and in a representative subgroup of 142 patients at long-term follow-up (LTFU; mean 3.0 years). Results: On-treatment HBsAg decline significantly varied according to HBV genotype (A and B more than C and D; P<0.001). On-treatment HBsAg decline also differed between patients with a combined response (n=43) and those without (n=178; 3.34 versus 0.69 log IU/ml decline at week 52; P<0.001). Among patients without a combined response, no difference was observed between HBeAg responders (n=41) versus non-responders (n=137). HBsAg decline was sustained in combined responders and progressed to 3.75 log IU/ml at LTFU. Patients with a combined response achieved pronounced HBsAg declines, irrespective of HBV genotype, and those who achieved HBsAg levels < 1,000 IU/ml at week 78 had a high probability of a sustained response and HBsAg clearance through LTFU. Conclusions: On-treatment HBsAg decline during PEG-IFN therapy for HBeAg-positive CHB depends upon HBV genotype. Patients with a combined response to PEG-IFN achieve a pronounced HBsAg decline, irrespective of HBV genotype, which is sustained through 3 years of off-treatment follow-up.

Introduction

Chronic hepatitis B (CHB) is an important global health problem, with >350 million people being chronically infected [1]. Prolonged liver inflammation due to infection with HBV may progress to cirrhosis, liver failure and hepatocellular carcinoma (HCC) [1,2]. Hepatitis B e antigen (HBeAg)-positive CHB is generally regarded as the earliest phase of infection in what is essentially a four-phase disease continuum [2]. Current treatment guidelines recommend both pegylated interferon (PEG-IFN) and nucleoside/nucleotide analogues (NA)
for the treatment of HBeAg-positive patients [2,3]. A 1-year course of PEG-IFN results in an off-treatment sustained response, defined as HBeAg loss and HBV DNA <10,000 copies/ml at 6 months post-treatment, in approximately 25% of patients [4,5]. Response to interferon (IFN)-based therapy has been reported to be associated with a lower incidence of HCC and prolonged survival [6–8].

Covalently closed circular DNA (cccDNA) is the main replication template of HBV [9] and low cccDNA levels following antiviral therapy have been shown to be predictive of a sustained response [10]. Intrahepatic cccDNA can only be assessed invasively, but it has recently been demonstrated that serum levels of hepatitis B surface antigen (HBsAg) reflect intrahepatic cccDNA levels in HBeAg-positive CHB patients and may consequently predict a sustained response [11–13].

PEG-IFN induces a strong decline in serum HBsAg levels in both HBeAg-positive and HBeAg-negative patients [14–18]. Patients who achieve a sustained response to PEG-IFN exhibit a steeper HBsAg decline compared with non-responders. A recent study among HBeAg-negative patients suggested that the degree of HBsAg decline may be influenced by the infecting HBV genotype as well [19]. Given these findings, a durable suppression of HBsAg may reflect immunological control over the virus. The long-term sustainability of PEG-IFN-induced HBsAg decline is, however, currently unknown. The aims of our study were therefore to investigate which factors are associated with HBsAg decline induced by PEG-IFN for HBeAg-positive CHB, and whether HBsAg decline is durable through long-term follow-up (LTFU).

Methods

Patients

Serum HBsAg levels were assessed in 221 HBeAg-positive CHB patients who were previously enrolled in an investigator-initiated multicentre randomized controlled trial and a subsequent LTFU study [4,20]. The inclusion and exclusion criteria for this study have been described elsewhere. In short, patients were eligible if they had been HBsAg-positive for ≥6 months prior to randomization, were HBeAg-positive twice within 8 weeks prior to randomization, had increased serum alanine aminotransferase (ALT) levels of 2–10× the upper limit of normal (ULN) and had a serum HBV DNA level >1.0×10⁵ copies/ml. Exclusion criteria were antiviral therapy within 6 months prior to randomization, viral coinfections, pre-existing cytopenia and/or decompensated liver disease. Patients were treated with PEG-IFN-α2b 100 µg weekly (Peglntron; Merck, Whitehouse Station, NJ, USA) in combination with a placebo or lamivudine (3TC) 100 mg (Zeffix; GlaxoSmithKline, Greenford, UK) daily for 52 weeks. The PEG-IFN dose was reduced to 50 µg per week after 32 weeks of therapy to limit the probability of early treatment discontinuation. Patients attended the outpatient clinic every 4 weeks for routine examinations and laboratory assessments during both the treatment and the post-treatment follow-up phase of the study. For the LTFU study, patients were re-evaluated at one additional visit at the local participating centre. The mean duration of follow-up was 3.0 years [20].

Inclusion criteria for the present study were completion of the 26-week follow-up phase of the main study and availability of a baseline serum sample for HBsAg quantification. Of the 266 patients in the initial study, 221 fulfilled these criteria. Of these patients, 142 participated in the associated LTFU study and had LTFU samples available for HBsAg quantification [20].

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. All patients gave written informed consent according to standards of the local ethics committees.

Laboratory measurements

Serum HBsAg was quantified in samples taken at baseline, during the treatment period (weeks 4, 8, 12, 24 and 52), during follow-up (week 78) and at LTFU using the ARCHITECT HBsAg assay (range 0.05–250 IU/ml; Abbott Laboratories, Abbott Park, IL, USA). HBV DNA quantification was performed using an in-house developed TaqMan PCR assay (lower limit of quantification 400 copies/ml) based on the EuroHep standard [21]. For the LTFU study, HBV DNA was measured with the Cobas TaqMan HBV assay (Roche Molecular Systems, Branchburg, NJ, USA), with a dynamic range of quantification of 174–6.4×10⁶ copies/ml (30–1.1×10⁵ IU/ml). There is an excellent correlation between the two assays [20]. ALT was measured locally in accordance with standard procedures and is presented as multiples of the ULN. HBV genotype was assessed using the INNO-LiPA assay (Inno-Path, Gent, Belgium).

Statistical analyses

Response to treatment was assessed at week 78 in all patients. A composite end point of HBeAg loss and HBV DNA level <10,000 copies/ml was chosen for definition of combined response [5], and patients who achieved HBeAg loss but failed to achieve HBV DNA <10,000 copies/ml were considered HBeAg responders. All others were non-responders. Associations between variables were tested using Student’s t-test, χ², Pearson correlation or their non-parametric equivalents when
appropriate. SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) and the SAS 9.2 programme (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

Patient characteristics

A total of 221 patients were included in this study. The mean age of the total study population was 34 years at the start of therapy, patients were predominantly male (78%) and of Caucasian origin (72%). HBV genotypes A and D were most prevalent in the study cohort (34% and 39%), followed by C (15%) and B (9%). Mean baseline ALT levels were 4.2×ULN, HBV DNA levels were 9.1 log copies/ml and HBsAg levels were 4.4 log IU/ml (Table 1). Of the 221 patients, 43 (19%) achieved a combined response (HBeAg negativity and HBV DNA <10,000 copies/ml at week 78).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Main study population (n=221)</th>
<th>LTFU study population (n=142)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
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<tr>
<td>Mean age, years (±sd)</td>
<td>34 (12)</td>
<td>34 (12)</td>
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</tr>
<tr>
<td>Male, n (%)</td>
<td>173 (78)</td>
<td>115 (81)</td>
<td>0.60</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (±sd)</td>
<td>25 (4.0)</td>
<td>25 (4.2)</td>
<td>0.66</td>
</tr>
<tr>
<td>Monotherapy, n (%)</td>
<td>111 (50)</td>
<td>75 (53)</td>
<td>0.63</td>
</tr>
<tr>
<td>Race</td>
<td>-</td>
<td>-</td>
<td>0.83</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>160 (72)</td>
<td>99 (70)</td>
<td>-</td>
</tr>
<tr>
<td>Asian, n (%)</td>
<td>44 (20)</td>
<td>30 (21)</td>
<td>-</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>17 (8)</td>
<td>13 (9)</td>
<td>-</td>
</tr>
<tr>
<td>Laboratory results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ALT ×ULN (±sd)</td>
<td>4.2 (3.0)</td>
<td>4.6 (3.4)</td>
<td>0.31</td>
</tr>
<tr>
<td>Mean HBV DNA, log copies/ml (±sd)</td>
<td>9.1 (0.89)</td>
<td>9.1 (0.80)</td>
<td>1.0</td>
</tr>
<tr>
<td>Mean HBsAg, log IU/ml (±sd)</td>
<td>4.4 (0.64)</td>
<td>4.3 (0.69)</td>
<td>0.26</td>
</tr>
<tr>
<td>HBV genotype</td>
<td>-</td>
<td>-</td>
<td>0.78</td>
</tr>
<tr>
<td>A, n (%)</td>
<td>74 (34)</td>
<td>41 (29)</td>
<td>-</td>
</tr>
<tr>
<td>B, n (%)</td>
<td>20 (9)</td>
<td>12 (9)</td>
<td>-</td>
</tr>
<tr>
<td>C, n (%)</td>
<td>32 (15)</td>
<td>27 (19)</td>
<td>-</td>
</tr>
<tr>
<td>D, n (%)</td>
<td>87 (39)</td>
<td>56 (39)</td>
<td>-</td>
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<tr>
<td>Other/mixed, n (%)</td>
<td>8 (4)</td>
<td>6 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Response at week 78</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Combined response, n (%)</td>
<td>43 (19)</td>
<td>24 (17)</td>
<td>0.58</td>
</tr>
<tr>
<td>HBeAg loss, n (%)</td>
<td>84 (38)</td>
<td>49 (35)</td>
<td>0.51</td>
</tr>
<tr>
<td>HBsAg loss, n (%)</td>
<td>19 (9)</td>
<td>10 (7)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

*Hepatitis B e antigen (HBeAg) loss and HBV DNA<10,000 copies/ml. *Includes those with a combined response. ALT, alanine aminotransferase; BMI, body mass index; HBsAg, hepatitis B surface antigen; LTFU, long-term follow-up; ULN, upper limit of normal.

HBsAg decline on-treatment

One year of treatment with PEG-IFN resulted in a mean decline in serum HBsAg levels of 1.17 log IU/ml. This decline was sustained through 6 months of post-treatment follow-up: the mean decline from baseline was 0.92 log IU/ml at week 78. At baseline, only age (P<0.01) and HBV genotype (P<0.01) were related to HBsAg decline at week 78 by univariate analysis. Combination therapy, ALT, log HBV DNA, sex and race were all not associated with HBsAg decline at week 78. By multivariate analysis, HBV genotype, age and log HBV DNA level at baseline were related to HBsAg decline at week 78.

HBsAg decline according to HBV genotype

Baseline HBsAg levels were significantly different in genotypes A through D. Mean HBsAg levels were 4.33 log IU/ml in patients with genotype A, 4.33 in genotype B, 3.79 in genotype C and 4.51 in genotype D (P<0.001 for genotype C versus other genotypes). Furthermore,
considerably different HBsAg decline patterns were observed in the respective genotypes. While patients with genotype D experienced a slight increase during the first 12 weeks of therapy, patients with genotypes A and B showed a strong initial decline (Figure 1). At the end of treatment, patients infected with genotypes A and B had a significantly more pronounced HBsAg decline (mean 1.90 and 2.17 log IU/ml, respectively), when compared to patients harbouring genotypes C or D (0.59 and 0.55, respectively; \( P < 0.001 \) for A and B versus C and D). Through post-treatment LTFU, considerable relapse was observed in patients with genotype B (decline at LTFU 1.24 log IU/ml), whereas HBsAg levels in patients with genotype A continued to decline (decline at LTFU 2.46 log IU/ml). HBsAg levels remained stable through LTFU in patients infected with genotypes C and D.

HBsAg decline according to treatment response

Pretreatment HBsAg levels were comparable in patients who achieved a combined response and in those who did not; 4.29 versus 4.43 log IU/ml (\( P = 0.19 \)). However, on-treatment HBsAg kinetics clearly differed between patients with a combined response and those without. Combined responders exhibited a decline of 3.34 log IU/ml, compared to 0.69 in all other patients (\( P < 0.001 \); Figure 2). Within the group who failed to achieve a combined response, no significant difference was observed between patients who achieved an HBeAg response (\( n = 41 \)) versus those who remained HBeAg-positive (\( n = 137 \)); mean declines were 0.90 and 0.62 log IU/ml at week 52, respectively (\( P = 0.17 \)). The HBsAg decline induced by PEG-IFN was sustained in patients with a combined response, and declined further through LTFU to 3.75 log IU/ml (\( P = 0.27 \) versus end of treatment). In those who were HBeAg-positive at week 78, mean HBsAg decline at LTFU was 0.51 log IU/ml (Figure 2; \( P < 0.001 \) compared with combined responders), whereas the HBeAg responders achieved a decline of 0.86 log IU/ml at LTFU (\( P = 0.35 \) versus those with positive HBeAg).

HBsAg decline according to treatment response and HBV genotype

Of the 43 combined responders, 42 were infected with genotype A through D (28 [65%] genotype A, 5 [12%] genotype B, 3 [7%] genotype C and 6 [14%] genotype D). Of the 41 HBeAg responders, 9 (22%) were infected with genotype A, 5 (12%) with B, 5 (12%) with C and 18 (44%) with D. Similar to the overall population, combined responders infected with genotypes A through D achieved a greater HBsAg decline than did patients...
with the same genotype who were HBeAg responders or who remained HBeAg-positive (Figure 3).

Combined responders experienced marked declines in HBsAg levels from baseline to end of treatment (genotype A 3.81 log IU/ml, genotype B 2.98 log IU/ml, genotype C 1.47 log IU/ml and genotype D 2.68 log IU/ml; \( P = 0.59 \)). At LTFU, declines were 4.18, 2.38, 1.87 and 3.09 log IU/ml in combined responders with genotypes A, B, C and D, respectively (\( P = 0.56 \)).

By contrast, on-treatment decline in the HBeAg responders (patients who cleared HBeAg but did not achieve HBV DNA <10,000 copies/ml) significantly varied according to HBV genotype; patients with genotype A and B achieved declines of 2.02 and 1.56 log IU/ml at week 52, compared to 0.50 and 0.43 log IU/ml in patients with C and D (\( P = 0.02 \) for A and B versus C and D). At LTFU, declines were 3.33, 0.92, 0.09 and 0.22 in HBeAg responders with genotypes A through D, respectively (\( P = 0.03 \)).

Relationship between HBsAg levels at week 78 and response at LTFU
A total of 33 of 142 (23%) patients with HBsAg data at LTFU achieved a combined response at LTFU. Analysis was limited to the 141 with available HBsAg levels at week 78. Probabilities of achieving a combined response at LTFU in relation to HBsAg levels and decline at week 78 are shown in Table 2, both for the overall population (\( n = 141 \)) and for patients with a combined response at week 78 with available LTFU data (\( n = 23 \)). Importantly, no patient without a decline at week 78 achieved HBsAg clearance by LTFU, whereas patients with an HBsAg level <1,000 IU/ml at week 78 (\( n = 28 \)) had a probability of HBsAg clearance of 46% (13/28). Only 2 of 113 (2%) patients with HBsAg ≥1,000 IU/ml achieved HBsAg clearance at LTFU. Among patients with a combined response, 73% (11/15) of those with HBsAg <1,000 IU/ml achieved HBsAg negativity at LTFU compared to 25% (2/8) of those with HBsAg ≥1,000 IU/ml.

Discussion
In this large study we show that on-treatment HBsAg decline is a sensitive marker for response to PEG-IFN, showing a steep decline in patients who achieved a combined response (defined as HBeAg loss and HBV DNA <10,000 copies/ml), irrespective of HBV...
genotype. A very limited decline was observed in patients who remained HBeAg-positive or those who cleared HBeAg but progressed to active HBeAg-negative CHB, and patients without an HBsAg decline at week 78 have a very limited probability of response at LTFU. Furthermore, HBsAg decline was sustained in patients with a combined response through 3 years of follow-up, reflecting a long-term sustained suppression after therapy discontinuation.

The HBV replication pathway that produces HBsAg is separate from the pathway that produces HBV DNA. HBsAg is transcribed and subsequently translated from the HBV envelope gene, and produced as small, medium or large HBsAg proteins [22,23]. Synthesized HBsAg proteins may then be incorporated into mature HBV nucleocapsids, and subsequently secreted from the hepatocyte. However, HBsAg production far exceeds that required for the production of HBV virions and HBsAg is therefore also secreted in the form of non-infectious particles. Commercially available HBsAg quantification assays probably detect all forms of HBsAg [24], but the clinical relevance of the different HBsAg forms is so far unclear.

HBsAg levels in the sera of patients with CHB depend on the phase of infection. Patients classified as being in the immune tolerant and immune clearance phases of the disease have the highest HBsAg levels, whereas HBsAg is lowest in inactive carriers [24–26]. Furthermore, patients classified as inactive carriers who experienced a subsequent HBV DNA increase (reactivation) had higher HBsAg levels compared to those who did not [25]. A post-treatment sustained reduction in HBsAg levels achieved with PEG-IFN therapy may therefore signify an immunological response, resulting in transition to the inactive carrier

Figure 3. HBsAg decline in patients with a combined response versus patients with an HBeAg response or no response by genotype

Combined response was defined as hepatitis B e antigen (HBeAg) loss and HBV DNA<10,000 copies/ml. HBeAg response was defined as HBeAg loss but HBV DNA>10,000 copies/ml. Response was assessed at week 78. Genotypes A, B, C and D are shown. Error bars represent the sem. HBsAg, hepatitis B surface antigen; LTFU, long-term follow-up.
HBsAg decline during PEG-IFN for HBeAg-positive CHB: LTFU

In our study, 1 year of PEG-IFN therapy induced a pronounced decline in serum HBsAg levels, particularly in patients who achieved HBeAg loss and HBV DNA<10,000 copies/ml at week 78. Importantly, the decline achieved in these combined responders was durable through LTFU. This implies not only long-term sustained disease remission with a very low probability of relapse [25], but also reflects the high probability of subsequent HBsAg loss as described previously in HBeAg-positive responders to PEG-IFN [20,27]. Furthermore, we found that patients who achieved a combined response (HBeAg clearance with HBV DNA<10,000 copies/ml at week 78) with concomitant HBsAg levels <1,000 IU/ml did not experience relapse during off-treatment follow-up and were very likely to clear HBsAg. Conversely, patients who failed to achieve an HBsAg decline from baseline by week 78 had little chance of combined response, and no chance of HBsAg loss, suggesting the necessity of retreatment with other agents.

The current study also shows that baseline HBsAg levels and on-treatment HBsAg decline in HBeAg-positive patients are dependent upon HBV genotype. These findings are in line with a report on HBeAg-negative subjects [19], and may reflect a difference in transcription efficacy between respective genotypes [28]. However, the differences observed in HBsAg decline according to genotype may also be a reflection of the variance in the efficacy of PEG-IFN across the genotypes. Among HBeAg responders, those with genotypes C and D experienced only a limited reduction in HBsAg levels, and these patients were reported to have a high probability of HBeAg seroreversion and persistently detectable HBV DNA through LTFU [20,29]. Conversely, HBeAg responders infected with genotype A experienced a pronounced decline in HBsAg levels, and also had the highest probability of losing HBsAg through LTFU [20]. Interestingly, we found detectable precore and/or core promoter mutants by INNO-LiPA line-probe assay in all but one of the HBeAg responders with available serum, irrespective of HBV genotype (n=29; data not shown). This suggests that the differences in HBsAg decline across genotypes are not due to the presence or absence of these mutants.

In contrast to the genotype specific differences among HBeAg responders, all combined responders experienced pronounced HBsAg declines. This shows that, irrespective of HBV genotype, a combined response is associated with a sustained reduction in HBsAg levels and a high probability of HBsAg loss through LTFU [27]. Taken together, these observations corroborate recent data highlighting the influence of HBV genotype on response to PEG-IFN, and show that a combined response of HBeAg loss and HBV DNA<10,000 copies/ml is the most appropriate marker for response to PEG-IFN, especially in patients with non-A genotypes [5,20].

Recent studies among HBeAg-positive [18] and HBeAg-negative [14,30] patients treated with PEG-IFN have shown that HBsAg levels during therapy may be used to predict response to treatment. However, the current study now shows that HBsAg decline during PEG-IFN treatment for HBeAg-positive CHB depends upon HBV genotype as well, and the differences in HBsAg decline suggest that genotype specific thresholds may be required when using HBsAg to guide PEG-IFN based therapy.

A possible caveat of our study is that we pooled data from the two treatment arms of the original trial. Combination therapy of PEG-IFN and 3TC is known to cause a slightly steeper on-treatment HBsAg decline. However, this effect of 3TC was the same regardless of treatment response or HBV genotype, and was not sustained post-treatment. Furthermore, we found no difference in any of the outcomes when we analysed the treatment arms separately. Response rates were similar in patients treated with PEG-IFN monotherapy versus the combination with 3TC (18% versus 21%; P=0.61), as was HBsAg decline at week 78 (0.86 versus 0.98 log IU/ml; P=0.63) and at LTFU (0.93 versus 1.32; P=0.22). A subgroup of non-responders was

<table>
<thead>
<tr>
<th>Response</th>
<th>All patients (n=141)*</th>
<th>Combined response (n=23)*</th>
</tr>
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<tr>
<td></td>
<td>Yes, n'</td>
<td>NPV, %</td>
</tr>
<tr>
<td>HBsAg at week 78</td>
<td></td>
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<tr>
<td>&lt;1,000 IU/ml</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>≥1,000 IU/ml</td>
<td>98</td>
<td>15</td>
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<tr>
<td>Any decline at week 78</td>
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<tr>
<td>Yes</td>
<td>71</td>
<td>31</td>
</tr>
<tr>
<td>No</td>
<td>38</td>
<td>1</td>
</tr>
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</table>

*All patients with hepatitis B surface antigen (HBsAg) levels at week 78 and at long-term follow-up (LTFU). Combined response was defined as hepatitis B e antigen (HBeAg) negativity with HBV DNA<10,000 copies/ml at week 78. Combined response at LTFU. NPV, negative predictive value; PPV, positive predictive value.
retreated after the initial study. Retreatment did not affect HBsAg kinetics during LTFU.

In conclusion, HBeAg-positive CHB patients who achieve a combined response (HBeAg loss and HBV DNA<10,000 copies/ml) to PEG-IFN therapy achieve a pronounced decline in HBsAg levels, irrespective of HBV genotype. By contrast, patients who clear HBeAg but have HBV DNA levels >10,000 copies/ml experience a limited decline, showing that HBeAg loss alone may be a suboptimal marker for response to PEG-IFN in patients with non-A genotypes. The HBsAg decline achieved in patients with a combined response is sustained through 3 years of post-treatment follow-up reflecting a durable response with a low chance of relapse and a high probability of subsequent HBsAg loss.

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HLA) received grants from and is a consultant for Bristol–Myers Squibb, Gilead Sciences, Novartis, Roche and Schering–Plough. SZ is a consultant for Bristol–Myers Squibb, Biolex, HGS, Merck/Schering–Plough, Novartis and Roche. EJH received funds for research and fees for consulting from Schering–Plough. VR is a consultant for Roche. All other authors declare no competing interests.

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