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A baseline tool for predicting response to peginterferon alfa-2a in HBeAg-positive patients with chronic hepatitis B

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Abstract

Background: Peginterferon induces off-treatment responses in approximately one-third of patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B.

Aims: To develop an easy-to-use baseline prediction score to identify hepatitis B virus (HBV) genotype B-/C-infected HBeAg-positive Asian patients likely to respond to peginterferon alfa-2a.

Methods: Generalised additive models, multiple logistic regression (MLR) analysis and internal validation methods were applied to data from 647 HBeAg-positive patients from China, Hong Kong and Taiwan to develop a scoring system to predict response 24 weeks after completing a 48-week course of peginterferon alfa-2a.

Results: Five baseline factors (age, sex, alanine aminotransferase ratio, hepatitis B surface antigen (HBsAg) level and HBV DNA level) were retained in the final MLR for HBeAg seroconversion and used to develop a scoring system from 0–7. Among patients with scores of 0-1, 2-3, 4 or ≥ 5 , HBeAg seroconversion was achieved in 6.4% (6/94), 23.0% (61/265), 36.4% (67/184) and 54.8% (57/104), respectively, and a combined response (HBeAg seroconversion plus HBV DNA $< 2,000$ IU/mL) in 5.3% (5/94), 12.8% (34/265), 25.0% (46/184) and 36.5% (38/104), respectively. Among patients with scores of 0-1, 2-3, 4 or ≥ 5 , 57.0% (53/93), 12.3% (31/253), 3.4% (6/178) and 1.0% (1/100) had HBsAg $\geq 20,000$ IU/mL at treatment Week 12; only 3/ 91 (3.3%) with HBsAg $\geq 20,000$ IU/mL experienced a combined response at 24 weeks post-treatment (negative predictive value = 97% [88/91]). **Conclusion:** A pre-treatment scoring system using readily available baseline characteristics identifies HBeAg-positive Asian patients likely to experience sustained HBeAg seroconversion after treatment with peginterferon alfa-2a.

Introduction

Chronic hepatitis B (CHB) is one of the most common chronic liver diseases and is a global health problem, being one of the leading causes of cirrhosis, hepatic decompensation, and hepatocellular carcinoma.¹ With a hepatitis B surface antigen (HBsAg) prevalence of 5.3%, it is estimated that approximately 95 million people have CHB in the Western Pacific Region (as defined by the World Health Organization), and that 75 million of these individuals reside in China.² Of the four common hepatitis B virus (HBV) genotypes, the most prevalent in China are genotype B (41%), which predominates in southern provinces, and genotype C (53%), which predominates in northern provinces.³

Serum hepatitis B e antigen (HBeAg) correlates with HBV infectivity and active replication,⁴ and is a major determinant of perinatal transmission of HBV.⁵ Recent guidelines suggest that sustained HBeAg seroconversion is a desirable treatment outcome in HBeAg-positive patients, as it is associated with an improved prognosis.^{4,6,7} Currently, there are two differing treatment strategies for HBeAg-positive CHB patients: long-term treatment with a nucleos(t)ide analogue or finite treatment with peginterferon alfa.^{4,6,7} While nucleos(t)ide analogues potentially inhibit HBV DNA replication, most patients require continuous therapy to maintain viral suppression.^{4,6,7} In contrast, a finite course of peginterferon induces off-treatment responses in approximately one-third of HBeAg-positive patients,^{8,9} and the response tends to be durable for years.¹⁰ The ideal treatment outcome is sustained HBsAg loss with or without seroconversion, as this endpoint is associated with remission of disease activity and improved long-term outcomes, including a reduced risk of progression to cirrhosis and hepatocellular carcinoma.⁴ However, as HBsAg loss is a rare event, more practical endpoints such as HBeAg seroconversion and HBV DNA suppression, which have been shown to be associated with long-term benefits such as a reduced risk of cirrhosis, hepatocellular carcinoma and liver-related death, and an increased probability of HBsAg loss, are used to define a successful treatment outcome.⁴

The ability to identify patients likely to respond to peginterferon would allow clinicians to exclude non-responders from therapy and minimise their exposure to the potential adverse effects of treatment. On-treatment decreases in HBV DNA^{11,12} and HBsAg¹³⁻¹⁷ levels at treatment Weeks 12 and 24 can be used as stopping rules. However, at present it is not possible to use baseline characteristics to select patients likely to respond to therapy. This is because the negative and positive predictive value of individual characteristics is not sufficient for this purpose, and it is not known whether a combination of baseline factors can be used to predict the outcome of treatment.^{8, 18,19} In order to address this gap in knowledge, we combined data from Asian HBeAg-positive, genotype B-/C-infected patients enrolled in three large phase III and IV studies, with the objective of developing a simple baseline

scoring system to estimate an individual patient's chance of responding to a finite course of treatment with peginterferon alfa-2a.

Patients and Methods

We performed a combined retrospective analysis of data from HBeAg-positive patients with CHB who received peginterferon alfa-2a (40KD) (PEGASYS®, F. Hoffmann-La Roche Ltd, Basel, Switzerland) at 180 µg/week for 48 weeks in a randomised, international phase III study (WV16240, Lau et al.⁸, NCT00048945), a randomised, international, phase IV study (WV19432, Liaw et al.⁹, NEPTUNE; NCT00435825) and a randomised, multi-centre, phase IV study conducted in Taiwan (ML21827, Su et al.²⁰ NCT00922207).

Patients eligible for these studies were required to be aged between 18 and 65 years, to have elevated serum alanine aminotransferase (ALT) levels during screening and to have an HBV DNA level during screening that was >500,000 copies/mL, in the study by Lau et al.,⁸ or >100,000 IU/mL in the NEPTUNE and NEED studies.^{9, 20} Patients were required to have a liver biopsy result consistent with the diagnosis of CHB to be included in the study by Lau et al.⁸ or Liaw et al.;⁹ however, a liver biopsy was not required for entry into the NEED study.

Patients with a history or evidence of decompensated liver disease, those co-infected with hepatitis C or D virus or HIV, and those who had received antiviral therapy for CHB within the previous 6 or 12 months, were excluded from these studies.^{8,9, 20}

Patients

Inclusion criteria

Patients included in the analysis had HBV genotype B or C infection and had been enrolled in study centres in China, Hong Kong or Taiwan; were included in the intention-to-treat population of the respective studies; had been randomised to 48 weeks' treatment with peginterferon alfa-2a 180 µg/week alone or in combination with 48 weeks of concomitant treatment with lamivudine (in the study by Lau et al.⁸), or with 6 weeks of concomitant treatment with adefovir or entecavir (in NEED²⁰); and had quantitative baseline data for serum HBsAg, HBV DNA and ALT levels. As no relevant differences in response among patients on peginterferon alfa-2a monotherapy and various combination therapies were observed in the two studies,^{8, 20} these patients were pooled together in this analysis.

Exclusion criteria

Patients who had been randomized to lamivudine alone in the phase III study and those randomised to a shorter duration of treatment (24 weeks), or a lower dosage of peginterferon alfa-2a (90 µg/week) in the NEPTUNE study, were excluded from the present analysis.

Outcome definition

Outcomes of interest in the present analysis included HBeAg seroconversion alone, or in combination with HBV DNA <2,000 IU/mL (combined response) 24 weeks and 48 weeks post-treatment. Patients with missing response data were treated as non-responders. The baseline predictor score was developed based on response at 24 weeks in the full dataset. However, HBeAg seroconversion and combined response data at 48 weeks post-treatment were also available for patients in the NEED study and for subsets of patients in the NEPTUNE and phase III studies who participated in follow-up studies. The ability of the baseline score to predict outcome at 48 weeks was evaluated in these patients.

Development of baseline predictor score

The baseline predictor score was developed in several steps. First, generalised additive models with the logit link were used to explore and visualise the relationship between each of the continuous variables and the two response variables at 24 weeks, and also to identify appropriate cut-offs for continuous variables to be used in the logistic regression analysis. In addition, the values of each factor were grouped by deciles and the empirical probabilities for response at the midpoints of the deciles were included in generalised additive model plots.

Associations between the baseline factors and treatment response were then explored by univariate logistic regression analyses. This included a search for the most statistically significant cut-off for each continuous baseline factor, which could be used to stratify patients into two subgroups corresponding to high and low response rates. Baseline factors considered in the analyses included: age, sex, ALT ratio (ALT divided by the upper limit of normal for the local laboratory), HBsAg level, and HBV DNA level. HBV genotyping is not routinely available in clinics in Asia, where HBV genotypes B and C are most prevalent; hence, genotype was not included as a baseline predictor during the development of the scoring system. In this study, a sensitivity analysis was performed to evaluate the predictive score separately in patients infected with HBV genotypes B and C.

Next, multiple logistic regression analyses were performed using a backward elimination process in which only factors associated with HBeAg seroconversion or combined response with a P value $< .25$ in the univariate logistic regression analysis were included. To allow for inclusion of factors with moderate predictive values, a P value of 0.1 was required in the backward selection procedure for a factor to remain in the model. The stability of the selected model was assessed by bootstrap resampling.²¹ A variable was considered to be a reliable predictor of response if it was selected in $\geq 50\%$ of 500 bootstrapped samples with replacement. The discrimination of the model was then quantified by calculating the area under the receiver operating characteristics (AUROC) curve, and the optimism-corrected AUROC curve were determined with bootstrap samples. The Hosmer-Lemeshow test was applied to assess the goodness-of-fit of the final model.

In the event that different predictors were identified for the two different outcomes, the model developed for HBeAg seroconversion was considered to be the primary model for the purposes of developing the scoring system. The scoring system was derived by assigning points according to the magnitude of the regression coefficient for predictive baseline characteristics retained in the multiple logistic regression models.²² A value of 0 points was assigned to the reference category for each predictive factor. Points were then assigned according to the size of the regression coefficient. The regression coefficient for HBV DNA ($>6-7.7 \log_{10}$ IU/mL) was used as the reference unit for 1 point with rounding to integer values.

The response rates by prediction scores were determined and exact 95% confidence intervals were calculated for the percentage of responders. Furthermore, the prediction characteristics' sensitivity, specificity, positive predictive value, negative predictive value, the positive likelihood ratio and the AUROC of the prediction score were determined for the two endpoints.

Results

Patients

A total of 1,652 patients were randomised to treatment in the three studies, of whom 647 Asian patients from China, Hong Kong and Taiwan with HBV genotype B or C infection were included in this analysis (279 from the NEED study, 68 from the NEPTUNE study and 300 from the phase III study). The reasons for exclusion from the analysis are shown in Supplementary Figure 1. The baseline characteristics of patients included in the analysis were broadly similar across the three studies (Table 1). Overall, the mean age was 34.2 years (range: 18-66 years), and the majority were male (72.2%). The mean ALT ratio was 4.1 x the upper limit of normal and the mean HBV DNA level was $8.5 \log_{10}$ IU/mL.

Among the 647 patients included in the analysis, 191 (29.5%) experienced HBeAg seroconversion, 155 (24.0%) had an HBV DNA level $<2,000$ IU/mL and 123 (19.0%) achieved a combined response after 24 weeks of untreated follow-up (Figure 1).

Graphic analysis and univariate logistic regression analysis to identify baseline predictive factors

The generalised additive model plots visualising the relationship between the continuous variables (age, ALT ratio, HBsAg level, HBV DNA level and treatment outcome; HBeAg seroconversion at 24 weeks post-treatment) showed a clear increase in response rates with decreasing age, decreasing HBsAg level, decreasing HBV DNA level (Supplementary Figure 2) and increasing ALT ratio. Based on these analyses and the univariate logistic regression analyses, the following data cut-offs were selected for further analysis: age <40 and ≥ 40 years; ALT ratio ≤ 4 and >4 x the upper limit of normal; HBsAg $\leq 25,000$ and $>25,000$ IU/mL; and, HBV DNA ≤ 6 , $>6-7.7$, and >7.7 $\log_{10}$ IU/mL.

The results of the univariate analysis of associations between baseline factors and the outcomes (HBeAg seroconversion and combined response) are shown in Table 2. HBeAg seroconversion and combined response rates are shown according to the selected cut-offs in Figure 2.

Multiple logistic regression analysis of response

Five baseline factors associated with HBeAg seroconversion and combined response in the univariate analysis with P values $<.25$ were included in the multiple logistic regression model selection procedure. All five of these factors (age, sex, ALT ratio, HBsAg level and HBV DNA level) remained significant after the backward selection process and were retained in the final model (Table 2). The covariates of the final multiple logistic regression models were selected in $\geq 70\%$ of the bootstrap samples

with the exception of ALT in the model for combined response, where it was selected in 58% of bootstrap samples; thus the models were quite stable. The area under the receiver operating characteristics curve (>0.66) and the Hosmer-Lemeshow test ($P>.15$) also indicate sufficient discrimination and goodness-of-fit. The scoring system was developed using the five factors retained in the final models, with points assigned according to the size of the regression coefficient (Table 2). The final scoring system for achieving a response ranges from 0 to 7, with higher scores indicating a higher likelihood of response (Table 3).

The distribution of baseline prediction scores in the 647 patients included in the analysis population was: 0 ($n = 13$, 2.0%); 1 ($n = 81$, 12.5%); 2 ($n = 122$, 18.9%); 3 ($n = 143$, 22.1%); 4 ($n = 184$, 28.4%); 5 ($n = 80$, 12.4%); 6 ($n = 24$, 3.7%); and 7 ($n = 0$).

Response according to predictive score

Response rates at 24 weeks generally increased with increasing baseline score and were lowest in patients with a score of 1 and highest in patients with a score of 6 (Supplementary Table 1). No patients had a baseline prediction score of 7 and too few patients had scores of 0 or 6 for a precise estimation of response rates. Among patients with baseline prediction scores of 0-3, HBeAg seroconversion rates at 24 weeks post-treatment ranged from 4.9% to 23.1%, and were below the overall rate of 29.5%. Conversely, among patients with baseline scores of 4-6, HBeAg seroconversion rates ranged from 36.4% to 58.3% and were above the rate for the overall population. The performance characteristics of the scoring system are provided in Supplementary Table 2.

Patients were placed into one of four groups according to baseline prediction score: 0-1, 2-3, 4 or 5-6. The rates of HBeAg seroconversion, and combined response at 24 weeks post-treatment were $<10\%$ in patients with a prediction score of 0-1 (negative predictive value $>90\%$) (Figure 3a). Among patients with baseline prediction scores

≥4 the rate of HBeAg seroconversion was 43.1% and the combined response rate was 29.2%. In the 519 patients with 48-week data, this baseline scoring system performed equally well: the AUROCs of the prediction score for HBeAg seroconversion at 24 and 48 weeks posttreatment were 0.689 and 0.711, respectively; the corresponding AUROCs for combined response were 0.676 at 24 weeks and 0.679 at 48 weeks post-treatment. In patients with a prediction score of 0-1, the rate of seroconversion at 48 weeks was 7.1% and combined response was 4.3%, while among those with a score ≥4 seroconversion was 47.2% and combined response was 28.2% (Figure 3b).

A total of nine out of 647 patients (1.4%) experienced HBsAg seroclearance at 24 weeks post-treatment, including one out of 94 (1.1%) with a baseline score of 0-1, five out of 265 (1.9%) with a baseline score of 2-3, two out of 184 (1.1%) with a baseline score of 4 and one out of 104 (1%) with a baseline score of 5-6.

Analysis of patients with HBV genotype B or C infection

HBeAg seroconversion at 24 weeks post-treatment was achieved in 29.6% (96/324) of patients with HBV genotype B infection and 29.5% (95/322) of patients with HBV genotype C infection (Supplementary Table 3). Among patients with baseline prediction scores of 0-1, 2-3, 4 and 5-6, HBeAg seroconversion was achieved by 6.0% (3/50), 26.4% (33/125), 36.6% (34/93) and 46.4% (26/56) of patients with HBV genotype B infection, respectively; and 7.0% (3/43), 20.0% (28/140), 36.3% (33/91) and 64.6% (31/48) of patients with HBV genotype C infection, respectively. A combined response was achieved by 4.0% (2/50), 16.0% (20/125), 29.0% (27/93) and 33.9% (19/56) of patients with HBV genotype B infection and baseline prediction scores of 0-1, 2-3, 4 and 5-6, respectively; and by 7.0% (3/43), 10.0% (14/140), 20.9% (19/91) and 39.6% (19/48) of patients with HBV genotype C infection and baseline prediction scores of 0-1, 2-3, 4 and 5-6, respectively.

Response rates 24 weeks post-treatment by baseline score and Week 12 and 24

HBsAg levels

A Week 12 quantitative HBsAg test result was available for a total of 624 patients, among whom 533 had an HBsAg level <20,000 IU/mL (85.4%) and 91 had an HBsAg level ≥20,000 IU/mL (14.6%). Among the 533 patients with HBsAg <20,000 IU/mL, 176 (33.0%) and 115 (21.6%) individuals achieved HBeAg seroconversion and a combined response, respectively; in the subset of 40 patients with HBsAg <20,000 IU/mL and prediction scores of 0-1, five (12.5%) achieved HBeAg seroconversion and four (10.0%) achieved a combined response. Among the 91 patients with HBsAg ≥20,000 IU/mL, nine (9.9%) and three (3.3%) individuals achieved HBeAg seroconversion and a combined response, respectively. The negative predictive value of an HBsAg level ≥20,000 IU/mL for a combined response was 95% (36/38) in patients with scores ≥2 and 97% (88/91) overall. The proportion of patients with baseline prediction scores of 0-1, 2-3, 4 and 5-6 and HBsAg ≥20,000 IU/mL at Week 12 was 57.0% (53/93), 12.3% (31/253), 3.4% (6/178) and 1.0% (1/100). No meaningful differences were seen between patients who received nucleos(t)ide analogues and those who did not (data not shown).

The association between the baseline prediction score and HBsAg level at Week 24 (categorized by 20,000 IU/mL) was similar (data not shown). The negative predictive value of HBsAg ≥20,000 IU/mL at Week 24 for combined response was 100% (57/57).

Discussion

The results of this analysis demonstrate that it is possible to identify HBeAg-positive CHB patients who are more likely or unlikely to respond to a finite course of peginterferon alfa-2a on the basis of a combination of baseline characteristics using a scoring system. The scoring system uses readily available demographic (age and sex) and laboratory data (ALT ratio, and HBsAg and HBV DNA levels), and could easily be incorporated into routine patient visits to inform treatment decisions, as recommended by international guidelines for the management and treatment of

HBV infection.^{4,6,7} As this score performs equally well in HBV genotype B- and C-infected patients, it eliminates the need for HBV genotyping, which is often not available in Asian centres.

The scoring system ranges from 0 to 7, with higher scores indicating a higher likelihood of response. We have grouped patients into four categories, taking into account the frequency of scores and response rates for adjacent scores. Patients with baseline prediction scores ≥ 4 comprised 45% of all patients included in the analysis; these had HBeAg seroconversion and combined response rates of 43% and 29%, respectively, at 24 weeks post-treatment. Among the group of patients with scores ≥ 4 , the highest response rates were obtained in those with scores of 5 or 6 (55% HBeAg seroconversion rate and 36% combined response rate). The score was developed based on data from 647 patients with 24-week post-treatment follow-up, and verified in a subset of 519 of these patients with 48-week follow-up. Thus, it appears that it is possible to identify patients with a good chance of achieving a sustained response. At the other end of the spectrum, patients with baseline prediction scores of 0-1 had the lowest likelihood of response. Fewer than 10% of these patients experienced HBeAg seroconversion or a combined response 24 and 48 weeks post-treatment. This is perhaps not surprising, given that more than one-half of patients in this category had an HBsAg level $\geq 20,000$ IU/mL at Week 12, which is recommended as a stopping rule for peginterferon.^{4,7} Patients with baseline prediction scores of 2-3 had an intermediate likelihood of achieving a sustained response, with a 21–23% rate of HBeAg seroconversion and 12–13% combined response rate at 24 and 48 weeks post-treatment. Treatment cannot automatically be recommended or discounted on the basis of these probabilities; however, the information could be used to inform treatment decisions.

Positive associations between certain baseline factors and treatment outcomes to peginterferon alfa have been reported previously.^{18, 23} In contrast to the present study, which focused on peginterferon alfa-2a, the most widely approved peginterferon for the treatment of CHB, most previous analyses have assumed that predictors of response are the same for both commercially available peginterferons and have pooled data from patients who received peginterferon alfa-2a and peginterferon alfa-2b. In addition, previous analyses have combined data from patients infected with HBV genotype A, the genotype associated with the best response to peginterferon, with data from patients infected with HBV genotype B or C. In general, factors associated with a sustained response (HBeAg loss and HBV DNA level <2,000 IU/mL at 24 weeks post-treatment) included: HBV genotype A infection, high serum ALT levels, low HBV DNA levels, low HBsAg levels, female sex, younger age, and absence of prior treatment with interferon.^{18, 23} When used alone, none of these factors has sufficient positive or negative predictive power to be used as the basis for treatment decisions.

The EPIC-B predictor model, which has been published in abstract form,²³ was able to identify patients with low (<20%) or high (>30%) chance of HBeAg loss with HBV DNA <2,000 IU/mL at 24 weeks post-treatment.

The model proposed here identifies patients with the highest probability of responding to peginterferon alfa-2a, but even so a substantial proportion of patients in the most favourable group did not achieve any response or achieved only seroconversion with HBV DNA remaining >2,000 IU/mL. One advantage of baseline prediction models, such as that in the present analysis, is that they can be combined with established on-treatment prediction tools to ensure that only patients with a good chance of response start therapy and only those with the highest likelihood of

response receive a full course of treatment. In this regard, the baseline prediction score was also predictive for the proportion of patients with HBsAg $\geq 20,000$ IU/mL at Weeks 12 and 24. In the present analysis, only three patients with an HBsAg level $\geq 20,000$ IU/mL at Week 12 achieved a combined response, and the negative predictive value of HBsAg $\geq 20,000$ IU/mL at Week 12 and 24 for HBeAg seroconversion and a combined response was $\geq 95\%$. The ability to identify patients unlikely to respond allows clinicians to minimise exposure to treatment and potential adverse events, and also conserves resources.

The strength of the proposed scoring system is that it adds to the knowledge of the combined influence of readily available baseline factors on the probability of a patient achieving a sustained post-treatment response. It does, however, have some limitations as a result of the retrospective nature of the analysis, and because the data were drawn from randomised controlled phase III and IV trials. Patients were highly selected and thus do not reflect the full spectrum of patients with CHB. In particular, patients with co-morbidities were excluded. The baseline prediction score does not appear to be associated with HBsAg loss at 24 weeks post-treatment; however, HBsAg loss is a rare event and longer durations of follow-up are required to draw firm conclusions with respect to this endpoint. As this score was designed specifically for use in Asian patients with HBV genotype B or C infection, it remains to be determined whether the scoring system can be applied to clinical practice in other geographic regions in populations with more diverse HBV genotype distributions. It also remains to be determined whether the model can be applied to treatment with peginterferon alfa-2b, which is approved for CHB in China.²⁴

In conclusion, the proposed scoring system uses readily available baseline characteristics to identify HBeAg-positive CHB patients with a high, moderate or low probability of achieving a sustained off-treatment response. The results show that the probability of sustained response is low in patients with scores ≤ 1 and that the probability of response increases in proportion to the baseline score, with a better

chance of achieving a sustained response in patients with scores ≥ 4 . Once validated, the score can be used effectively by clinicians to select patients for finite treatment with peginterferon alfa-2a. In practice, a baseline scoring system will allow clinicians to identify which patients are likely or unlikely to respond to a finite course of treatment with peginterferon alfa-2a, avoiding unnecessary treatment, and thus adverse events, in those patients unlikely to experience treatment success.

References

1. Chan HL, Hui AY, Wong ML, et al. Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma. *Gut*. 2004;53:1494-1498.
2. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet*. 2015;386:1546-1555.
3. Zeng G, Wang Z, Wen S, et al. Geographic distribution, virologic and clinical characteristics of hepatitis B virus genotypes in China. *J Viral Hepat*. 2005;12:609-617.
4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. *J Hepatol*. 2012;57:167-185.
5. Ott JJ, Stevens GA, Wiersma ST. The risk of perinatal hepatitis B virus transmission: hepatitis B e antigen (HBeAg) prevalence estimates for all world regions. *BMC Infect Dis*. 2012;12:131.
6. Terrault NA, Bzowej NH, Chang K, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016;63:261-283.
7. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int*. 2016;10:1-98.
8. Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2005;352:2682-2695.

9. Liaw YF, Jia JD, Chan HL, et al. Shorter durations and lower doses of peginterferon alfa-2a are associated with inferior hepatitis B e antigen seroconversion rates in hepatitis B virus genotypes B or C. *Hepatology*. 2011;54:1591-1599.
10. Wong VW, Wong GL, Yan KK, et al. Durability of peginterferon alfa-2b treatment at 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology*. 2010;51:1945-1953.
11. Flink HJ, van Zonneveld M, Hansen BE, de Man RA, Schalm SW, Janssen HL. Treatment with Peg-interferon α -2b for HBeAg-positive chronic hepatitis B: HBsAg loss is associated with HBV genotype. *Am J Gastroenterol*. 2006;101:297-303.
12. Fried MW, Piratvisuth T, Lau GK, et al. HBeAg and hepatitis B virus DNA as outcome predictors during therapy with peginterferon alfa-2a for HBeAg-positive chronic hepatitis B. *Hepatology*. 2008;47:428-434.
13. Piratvisuth T, Marcellin P, Popescu M, Kapprell HP, Rothe V, Lu ZM. Hepatitis B surface antigen: association with sustained response to peginterferon alfa-2a in hepatitis B e antigen-positive patients. *Hepatol Int*. 2013;7:429-436.
14. Sonneveld MJ, Rijckborst V, Boucher CA, Hansen BE, Janssen HL. Prediction of sustained response to peginterferon alfa-2b for hepatitis B e antigen-positive chronic hepatitis B using on-treatment hepatitis B surface antigen decline. *Hepatology*. 2010;52:1251-1257.
15. Sonneveld MJ, Hansen BE, Piratvisuth T, et al. Response-guided peginterferon therapy in hepatitis B e antigen-positive chronic hepatitis B using serum hepatitis B surface antigen levels. *Hepatology*. 2013;58:872-880.
16. Chan H, Wong V, Chim A, Chan H, Wong G, Sung J. Serum HBsAg quantification to predict response to peginterferon therapy of e antigen positive chronic hepatitis B. *Aliment Pharmacol Ther*. 2010;32:1323-1331.
17. Peng C, Lai H, Li Y, Su W, Chuang P, Kao J. Early serum HBsAg level as a strong predictor of sustained response to peginterferon alfa-2a in HBeAg-negative chronic hepatitis B. *Aliment Pharmacol Ther*. 2012;35:458-468.

18. Buster EH, Hansen BE, Lau GK, et al. Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon-alfa. *Gastroenterology*. 2009;137:2002-2009.
19. Janssen HL, van Zonneveld M, Senturk H, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet*. 2005;365:123-129.
20. Su WW, Hsu CW, Lee CM, et al. Combination therapy with peginterferon alfa-2a and a nucleos(t)ide analogue for HBeAg-positive chronic hepatitis B patients: results of a large, randomised, multicentre, double-blind, placebo-controlled study. *J Hepatol*. 2014;60 (Suppl.):S47 (Abstract O113).
21. Steyerberg E. Clinical Prediction Models. A Practical Approach to Development, Validation, and Updating. New York: Springer-Verlag; 2009.
22. Sullivan LM, Massaro JM, D'Agostino RB Sr. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. *Stat Med*. 2004;23:1631-1660.
23. Sonneveld MJ, Wong VW, Cheng J, et al. Estimating the probability of response to peginterferon alfa in HBeAg-positive chronic hepatitis B: the Epic-B Predictor. *J Hepatol*. 2014;60:S423-S424.
24. Cheng J, Wang Y, Hou J, et al. Peginterferon alfa-2b in the treatment of Chinese patients with HBeAg-positive chronic hepatitis B: a randomized trial. *J Clin Virol*. 2014;61:509-516.

Statement of Interests

H. L. Y. Chan has served on advisory committees or review panels or been a speaker for AbbVie, Gilead, MSD, BMS, Roche, Novartis, and Echosens. D. Messinger is an employee of Prometris GmbH, who have a contract with F. Hoffmann-La Roche Ltd to provide statistical support. G. V. Papatheodoridis has served on advisory committees or review panels or been a speaker for AbbVie, Boehringer Ingelheim, BMS, Gilead, GSK, Janssen, MSD, Novartis and Roche and has received research

support from AbbVie, BMS, Gilead, Janssen and Roche. M. Cornberg has been a consultant for Roche, Gilead and BMS and has received research support from Roche. T. Piratvisuth has served on advisory boards or been a speaker for Roche, BMS, MSD, Novartis and GSK and has received research support from Roche, BMS, MSD, Novartis, Fibrogen and Bayer. A. Thompson has served on advisory boards and received research support from Roche. A. Caputo is an employee of Roche S.p.A. G. Bakalos is employee of F. Hoffmann-La Roche Ltd. V. Pavlovic was an employee of Roche Products Ltd at the time the research was carried out. P. Lampertico has served on advisory committees or review panels or been a speaker for BMS, Roche, Gilead, GSK and MSD. H. Ren, P Kennedy and Q Xie have nothing to disclose. This research was funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Writing support was provided by Manda Gent, PhD, and Blair Jarvis, MSc, of Health Interactions and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Tables

TABLE 1 Baseline characteristics

Characteristic	Phase IV NEED study Peginterferon alfa-2a 180 µg/week ± adefovir or entecavir x 48 weeks (n = 279)	Phase IV NEPTUNE Follow-up study Peginterferon Alfa-2a 180 µg/week x 48 weeks (n = 68)	Phase III Study ^(8, 9) Peginterferon alfa-2a 180 µg/week ± lamivudine x 48 weeks (n = 300)	Total (N = 647)
Age, years, mean (±SD)	38.2 (9.8)	33.0 (9.6)	30.8 (8.7)	34.2 (9.9)
Male sex, n (%)	199 (71.3)	37 (54.4)	231 (77.0)	467 (72.2)
HBV genotype, n (%)				
B	167 (59.9)	36 (52.9)	121 (40.3)	324 (50.1)
B/C	–	–	1 (0.3)	1 (0.2)
C	112 (40.1)	32 (47.1)	178 (59.3)	322 (49.8)
ALT ratio x ULN, mean (±SD)	4.8 (5.0)	3.0 (3.1)	3.8 (3.0)	4.1 (4.0)
HBsAg, log ₁₀ IU/mL, mean (±SD)	3.9 (0.8)	3.8 (0.6)	4.1 (0.7)	4.0 (0.7)
HBV DNA, log ₁₀ IU/mL, mean (±SD)	7.7 (1.1)	7.4 (1.1)	9.4 (2.1)	8.5 (1.8)

ALT ratio = alanine aminotransferase level divided by the upper limit of normal (ULN) for the local laboratory.

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; SD, standard deviation; ULN, upper limit of normal.

TABLE 2 Univariate and multiple logistic regression analysis of factors associated with HBeAg seroconversion and the combination of HBeAg seroconversion and HBV DNA <2,000 IU/mL at 24 weeks post-treatment

		Univariate Logistic Regression				Final Multiple Logistic Regression Model				Selected in Bootstrap Models
Baseline Characteristic		Regression Coefficient	Odds Ratio (95% CI)	P Value*	P Value (Effect)**	Regression Coefficient	Odds Ratio (95% CI)	P value*	P value (Effect)* *	
HBeAg seroconversion at 24 weeks post-treatment										
Age, <40 vs. ≥40 years		0.4728	1.605 (1.069-2.407)	0.0223	0.0223	0.5999	1.822 (1.188-2.795)	.0060	0.0060	86%
Sex, female vs. male		0.4251	1.530 (1.060-2.207)	0.0230	0.0230	0.4351	1.545 (1.049-2.276)	.0277	0.0277	72%
ALT ratio x ULN, >4 vs. ≤4		0.5406	1.717 (1.212-2.432)	0.0023	0.0023	0.7672	2.154 (1.476-3.144)	<.0001	≤0.0001	99%
HBsAg (IU/mL), ≤25,000 vs.>25,000		1.0163	2.763 (1.797-4.248)	<0.0001	<0.0001	0.8935	2.444 (1.526-3.912)	.0002	0.0002	99%
HBV DNA (log ₁₀ IU/mL)	>6–7.7 vs. >7.7	0.7323	2.080 (1.413-3.062)	0.0002	<0.0001	0.5722	1.772 (1.158-2.712)	.0084	0.0002	98%
	≤6 vs. >7.7	1.2544	3.506 (1.842-6.670)	0.0001		1.2843	3.612 (1.823-7.156)	.0002		
						AUROC = 0.692, optimism-corrected AUROC = 0.676, Hosmer-Lemeshow P value=0.15				
HBeAg seroconversion and HBV DNA <2,000 IU/mL at 24 weeks post-treatment										
Age, <40 vs. ≥40 years		0.7440	2.104 (1.258-3.521)	0.0046	0.0046	0.8682	2.383 (1.403-4.046)	0.0013	0.0013	96%
Sex, male vs. female		0.5083	1.662 (1.097-2.520)	0.0166	0.0166	0.4863	1.626 (1.057-2.502)	0.0270	0.0270	73%
ALT ratio x ULN, >4 vs. ≤4		0.2781	1.321 (0.882-1.978)	0.1774	0.1774	0.4226	1.526 (0.990-2.351)	0.0554	0.0554	58%
HBsAg (IU/mL), ≤25,000 vs.>25,000		0.9055	2.473 (1.481-4.129)	0.0005	0.0005	0.7933	2.211 (1.269-3.850)	0.0051	0.0051	93%

HBV DNA (log ₁₀ IU/mL)	>6–7.7 vs. >7.7	0.6806	1.975 (1.272-3.066)	0.0024	0.0007	0.5257	1.692 (1.049-2.729)	0.0312	0.0129	84%
	≤6 vs. >7.7	1.0275	2.794 (1.399-5.579)	0.00366		0.9549	2.598 (1.240-5.446)	0.0114		
						AUROC = 0.684, optimism-corrected AUROC = 0.660, Hosmer-Lemeshow <i>P</i> value=0.64				

* Wald chi-square test for each regression coefficient; ** Wald chi-square test for each variable.

ALT ratio = alanine aminotransferase level divided by the upper limit of normal (ULN) for the local laboratory.

ALT, alanine aminotransferase; AUROC, area under the receiver operating characteristics curve; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ULN, upper limit of normal.

TABLE 3 Scoring system for predictive baseline characteristics

Characteristic		Score
Age, years	≥40	0
	<40	1
Gender	Male	0
	Female	1
ALT ratio x ULN	≤4	0
	>4	1
HBsAg, IU/mL	>25,000	0
	≤25,000	2
HBV DNA, log ₁₀ IU/mL	>7.7	0
	>6–7.7	1
	≤6	2

ALT ratio = alanine aminotransferase level divided by the upper limit of normal (ULN) for the local laboratory.

A, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ULN, upper limit of normal.

Figure legends

FIGURE 1 Overall response rates in 647 patients 24 weeks post-treatment.

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

FIGURE 2 HBeAg seroconversion (A) and combined response (B) 24 weeks post-treatment by baseline characteristic. *P* values are based on the univariate regression analysis.

Combined response = HBeAg seroconversion and HBV DNA <2,000 IU/mL.

ALT ratio = alanine aminotransferase level divided by the upper limit of normal (ULN) for the local laboratory. HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ULN, upper limit of normal.

FIGURE 3 HBeAg seroconversion and combined response rates (A) at 24 weeks post-treatment and (B) at 48 weeks post-treatment, according to baseline predictor score

A

B

Fig 3

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

Supporting Information

Supplementary Table 1. Response Rates After 24 Weeks Post-Treatment by Baseline Predictor Score

Predictor	n/N (%)	HBeAg	HBV DNA <2,000	Combined
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Score		Seroconversion n/N (%)	IU/mL n/N (%)	Response n/N (%)
0	13/647 (2.0)	2/13 (15.4)	3/13 (23.1)	2/13 (15.4)
1	81/647 (12.5)	4/81 (4.9)	6/81 (7.4)	3/81 (3.7)
2	122/647 (18.9)	28/122 (23.0)	24/122 (19.7)	17/122 (13.9)
3	143/647 (22.1)	33/143 (23.1)	24/143 (16.8)	17/143 (11.9)
4	184/647 (28.4)	67/184 (36.4)	55/184 (29.9)	46/184 (25.0)
5	80/647 (12.4)	43/80 (53.8)	33/80 (41.3)	28/80 (35.0)
6	24/647 (3.7)	14/24 (58.3)	10/24 (41.7)	10/24 (41.7)
All	647/647 (100)	191/647 (29.5)	155/647 (24.0)	123/647 (19.0)

Combined response = HBeAg seroconversion and HBV DNA <2,000 IU/mL.

Abbreviations: HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

Supplementary Table 2. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive likelihood ratio for the two endpoints

Prediction	True		False		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Positive likelihood ratio
Score	Positive	Negative	Positive	Negative					
HBeAg seroconversion									
≥1	189	11	445	2	99.0	2.4	29.8	84.6	1.01
≥2	185	88	368	6	96.9	19.3	33.5	93.6	1.20
≥3	157	182	274	34	82.2	39.9	36.4	84.3	1.36
≥4	124	292	164	67	64.9	64.0	43.1	81.3	1.81
≥5	57	409	47	134	29.8	89.7	54.8	75.3	2.90
≥6	14	446	10	177	7.3	97.8	58.3	71.6	3.34
Combined response									
≥1	121	11	513	2	98.4	2.1	19.1	84.6	1.01
≥2	118	89	435	5	95.9	17.0	21.3	94.7	1.16
≥3	101	194	330	22	82.1	37.0	23.4	89.8	1.30
≥4	84	320	204	39	68.3	61.1	29.2	89.1	1.75
≥5	38	458	66	85	30.9	87.4	36.5	84.3	2.45
≥6	10	510	14	113	8.1	97.3	41.7	81.9	3.04

Sensitivity = $100 \times \text{true positive} / (\text{true positive} + \text{false negative})$; Specificity = $100 \times \text{true negative} / (\text{true negative} + \text{false positive})$; PPV = $100 \times \text{true positive} / (\text{true positive} + \text{false positive})$; NPV = $100 \times \text{true negative} / (\text{true negative} + \text{false negative})$; Positive likelihood ratio = $\text{Sensitivity} / (100 - \text{Specificity})$.

Combined response = HBeAg seroconversion and HBV DNA <2,000 IU/mL.

Abbreviation: HBeAg, hepatitis B e antigen.

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Supplementary Table 3. Response Rates 24 Weeks Post-Treatment by Baseline Score and HBV Genotype

Prediction Score	Genotype B (n=324)				Genotype C (n=322)			
	n (%)	HBeAg Seroconversion n/N (%)	HBV DNA <2,000 IU/mL n/N (%)	Combined Response n/N (%)	n (%)	HBeAg Seroconversion n/N (%)	HBV DNA <2,000 IU/mL n/N (%)	Combined Response n/N (%)
0	5 (1.5)	1/5 (20.0)	1/5 (20.0)	1/5 (20.0)	8 (2.5)	1/8 (12.5)	2/8 (25.0)	1/8 (12.5)
1	45 (13.9)	2/45 (4.4)	4/45 (8.9)	1/45 (2.2)	35 (10.9)	2/35 (5.7)	2/35 (5.7)	2/35 (5.7)
2	70 (21.6)	16/70 (22.9)	15/70 (21.4)	10/70 (14.3)	52 (16.1)	12/52 (23.1)	9/52 (17.3)	7/52 (13.5)
3	55 (17.0)	17/55 (30.9)	15/55 (27.3)	10/55 (18.2)	88 (27.3)	16/88 (18.2)	9/88 (10.2)	7/88 (8.0)
4	93 (28.7)	34/93 (36.6)	33/93 (35.5)	27/93 (29.0)	91 (28.3)	33/91 (36.3)	22/91 (24.2)	19/91 (20.9)
5	43 (13.3)	19/43 (44.2)	17/43 (39.5)	13/43 (30.2)	37 (11.5)	24/37 (64.9)	16/37 (43.2)	15/37 (40.5)
6	13 (4.0)	7/13 (53.8)	6/13 (46.2)	6/13 (46.2)	11 (3.4)	7/11 (63.6)	4/11 (36.4)	4/11 (36.4)
Total	324	96/324 (29.6)	91/324 (28.1)	68/324 (21.0)	322	95/322 (29.5)	64/322 (19.9)	55/322 (17.1)

Abbreviations: HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

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