Editorial: a baseline tool for predicting response to peginterferon alfa-2a in HBeAg-positive patients—same score, different outcomes

Peginterferon alfa-2a is the first-line therapy of chronic hepatitis B (CHB) recommended by current treatment guidelines.\(^1\)\(^{-3}\) The advantages of peginterferon include a finite duration of therapy, higher rates of hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) seroconversion and lack of anti-viral resistance. However, peginterferon alfa-2a is only effective in approximately one-third of HBeAg-positive patients.\(^1\)\(^{-3}\) Thus, it is desirable to identify likely responders before the initiation of therapy to spare non-responders from futile treatment.

In a recent issue of *Alimentary Pharmacology and Therapeutics*, Chan et al identified five baseline factors (age, sex, alanine aminotransferase ratio, HBsAg level and HBV DNA level) significantly associated with HBeAg seroconversion or HBeAg seroconversion with HBV DNA <2000 IU/mL (combined response) at 24 weeks post-treatment through multiple logistic regression analysis. They developed a scoring system with a score of 0-7 to predict the likelihood of response in genotype B- or C-infected HBeAg-positive Asian patients.\(^4\) Patients with a baseline score of 0-1, 2-3, 4 and ≥5 had HBeAg seroconversion and combined response rates of 6.4% and 5.3%, 23% and 12.8%, 36.4% and 25% and 54.8% and 36.5%, respectively, at 24 weeks post-treatment. They further validated the predictive role of this scoring system in 519 patients with available data at 48 weeks post-treatment and demonstrated its comparable performance. The baseline score was also correlated with the likelihood of achieving HBsAg <20 000 IU/mL at 12 weeks of therapy. Thus, the proposed scoring system is a convenient tool which assists clinicians in estimating the likelihood of sustained response to peginterferon alfa-2a and thereby select potential responders for treatment.

An important question that may affect the clinical usefulness of this scoring system is its ability to discriminate between two distinct outcomes (HBV DNA ≥2000 IU/mL vs <2000 IU/mL) among patients who achieve HBeAg seroconversion. Sixty-eight of 647 (10.5%) achieved HBeAg seroconversion with HBV DNA ≥2000 IU/mL at 24 weeks post-treatment. Patients who evolved to HBeAg-negative CHB despite achieving HBeAg seroconversion following peginterferon therapy should be regarded as treatment failures. In fact, a baseline score of 0-1, 2-3, 4 and ≥5 predicted 1.1%, 10.2%, 11.4% and 18.3% chance, respectively, for HBeAg seroconversion with HBV DNA ≥2000 IU/mL at 24 weeks post-treatment. Therefore, this baseline scoring system may mainly identify patients who are likely to achieve HBeAg seroconversion but does not discriminate or take into regard the possibility of HBeAg seroconversion accompanied by HBV DNA >2000 IU/mL post seroconversion. The authors have not identified the baseline and on-treatment clinical and virological features that distinguished patients who achieved HBeAg seroconversion with HBV DNA <2000 IU/mL from those who achieved HBeAg seroconversion with HBV DNA ≥2000 IU/mL to propose any additional on-treatment stopping rule to spare the latter patients from further treatment. A possible clue might be the relative abundance and distinct evolution of the precore or basal core promoter mutants among these patients.\(^5\)\(^{-6}\) Further study is warranted to improve the predictive performance of this scoring system.

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**LINKED CONTENT**

This article is linked to Chan et al and Chan papers. To view these articles visit https://doi.org/10.1111/apt.14862 and https://doi.org/10.1111/apt.14961.
Editorial: a baseline tool for predicting response to peginterferon alfa-2a in HBeAg-positive patients—same score, different outcomes. Author's Reply

We appreciate the comments that our baseline predictive score was not designed to differentiate patients who would have active or inactive viraemia after hepatitis B e antigen (HBeAg) seroconversion with peginterferon therapy. However, the primary purpose of a baseline predictive score is to select the right patient for treatment, and our score can achieve this purpose.

Among patients who have a high predictive score, they have a higher chance to develop HBeAg seroconversion as well as a combined response, which was defined as HBeAg seroconversion and hepatitis B virus (HBV) DNA < 2000 IU/mL at week 24 posttreatment. Our score was further validated by 48-week posttreatment results. Hence, this score can facilitate clinicians to select patients who have a higher chance of response to receive peginterferon treatment and communicate with patients their approximate chance of response, both in terms of HBeAg seroconversion and combined response. For example, patients who have a predictive score ≥5 will have 54.8% chance of HBeAg seroconversion and 36.6% chance of combined response at week 24 posttreatment, and most of them will have response sustained till week 48 posttreatment. These patients would favour the choice of peginterferon as first-line antiviral treatment. On-treatment stopping rules by hepatitis B surface antigen (HBsAg) levels at week 12 and 24 should still be used after peginterferon is started. In HBeAg-positive patients infected by genotype B and C HBV received peginterferon therapy, approximately 20% patients may have HBsAg > 20 000 IU/mL at week 12, which has a high predictive value for nonresponse. Nonetheless, even with on-treatment predictive biomarkers, it is impossible to accurately differentiate patients who will undergo HBeAg seroconversion with HBV DNA > 2000 IU/mL vs <2000 IU/mL posttreatment.

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