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EDITORIAL

Are we ready to use the hepatitis B surface antigen level to guide peginterferon treatment in HBeAg-negative chronic hepatitis B?

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In chronic hepatitis B virus (HBV) infection, hepatitis B e antigen (HBeAg) seroconversion often indicates host immune clearance. Approximately 30 % of patients, however, still have active viremia and fluctuating alanine aminotransferase (ALT) levels in the HBeAg-negative phase [1]. These patients with HBeAg-negative chronic hepatitis B probably have an immune escape by the virus; a further attempt of immune modulator therapy by interferon might be difficult and the post-treatment relapse rate is high. Early experience in Europe using 12-month interferon-alpha combined with lamivudine only yielded a sustained viral suppression (undetectable by nonpolymerase chain reaction assay) rate of approximately 15 % at 6–12 months post-treatment [2, 3]. With 12-month peginterferon alfa-2a with/without lamivudine combination in the phase III international trial for HBeAg-negative chronic hepatitis B, approximately 22.6 % of patients could achieve sustained viral suppression to $\leq$10,000 copies/ml at 3-year post-treatment [4]. Owing to the inconvenient subcutaneous route of administration, potential adverse effects, and a high drug cost of peginterferon, one should select patients who have a higher chance of response to the peginterferon therapy. On the other hand, peginterferon is not preferred or should be stopped earlier if the chance of response is too low.

On post hoc analysis of the phase III trial of peginterferon alfa-2a (with/without lamivudine combination), HBeAg-negative patients at a younger age and those who had lower HBV DNA at baseline had a higher chance of achieving a response, which was defined as HBV DNA $\leq$20,000 copies/ml at 24-week post-treatment [5]. Patients infected by genotype C HBV also have a better response than those infected by genotype D HBV. Nonetheless, the differences in response between patients with different baseline predictive factors were too small to guide patient selection for treatment. For example, the mean baseline HBV DNA was 7.1 log copies/ml among responders versus 7.5 log copies/ml among relapsers. Better response predictors for peginterferon treatment are therefore warranted.

Serum hepatitis B surface antigen (HBsAg) quantification is a very hot topic of research in recent years. The level of serum HBsAg has been shown to reflect the level and transcriptional activity of covalently closed circular (ccc) DNA [6]. However, among HBeAg-negative patients, the relationship between serum HBsAg level and cccDNA is much weaker than that in HBeAg-positive patients [7]. The exact reason for this observation is uncertain, but could be related to the production of HBsAg by integrated HBV surface gene fragments in the host chromosome or the uncoupling on the regulation of HBsAg and HBV DNA production after HBeAg seroconversion. Nonetheless, in natural history studies, a lower HBsAg level is associated with inactive hepatitis [8, 9] and a higher chance of spontaneous seroclearance of HBsAg [10], suggesting that a lower HBsAg level is associated with better immune control of the virus.

In this issue of the Journal, Marcellin et al. [11] reported the use of serum HBsAg as the on-treatment response predictor to peginterferon alfa-2a with/without lamivudine combination in HBeAg-negative patients. This was a subgroup analysis of 120 patients who had HBsAg levels available for analysis among the original cohort of 230 patients in the phase III trial. Efficacy in terms of HBV

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DNA ≤2,000 IU/ml and HBsAg seroclearance at 1 and 5 years post-treatment were assessed as endpoints. Baseline HBsAg at a cut-off of 5,000 IU/ml had positive and negative predictive values of 34 and 78 % for the HBV DNA response at 1 year and 30 and 80 % for the HBV DNA response at 5-year post-treatment, respectively. A ≥10 % reduction in the log HBsAg level at weeks 12 and 24 could predict post-treatment responses to peginterferon. Comparing patients who had ≥10 versus <10 % reduction in log HBsAg at week 24, 35.8 versus 13.2 % of patients had an HBV DNA level of ≤2,000 IU/ml and 22.4 versus 3.8 % of patients had HBsAg seroconversion at 5-year post-treatment.

Based on the results of this study, the HBsAg level at baseline is not good enough as a stand-alone marker to guide patient selection for peginterferon treatment [11]. In this study, the investigators have not explored whether the HBsAg level has any additional value to the conventional baseline predictive factors such as age, HBV DNA level, and HBV genotype. In natural history studies among untreated patients, an HBsAg level of <1,000 IU/ml seems to be a prerequisite and an HBsAg level of <100 IU/ml is a good predictor of HBsAg seroclearance [10]. Furthermore, patients who have an HBV DNA level of <2,000 IU/ml and an HBsAg level of <100 IU/ml have the highest chance of clearing HBsAg in subsequent years of follow-up. It is therefore reasonable to believe that patients who have lower baseline HBV DNA and HBsAg levels will have a stronger immune response to the peginterferon therapy. Future research is needed to explore whether the addition of baseline serum HBsAg quantification can improve the prediction of response to peginterferon in HBeAg-negative patients.

From the experience of HBeAg-positive chronic hepatitis B, HBsAg level is a useful on-treatment monitoring tool to predict the response to peginterferon. In essence, a lower absolute HBsAg level at weeks 12 and 24 of peginterferon therapy is associated with a higher chance of sustained HBeAg seroconversion post-treatment [12]. In the current report by Marcellin et al. [11], a ≥10 % reduction in log HBsAg at weeks 12 and 24 was found to be the best predictor of the post-treatment response, but no absolute HBsAg level could be identified as a useful response predictor. Similarly, a small study in France also found that an early reduction of the HBsAg level by 0.5 log IU/ml, but not an absolute HBsAg level, could predict the virological response 6-month post-treatment [13]. The reason behind the conflicting observations between HBeAg-positive and HBeAg-negative patients is largely unknown. One possibility is a very wide range of HBsAg levels in HBeAg-negative patients; some patients can have a very low HBsAg level but yet active disease. In a previous report among 19 HBeAg-negative patients with active disease (elevated ALT and/or HBV DNA >10,000 copies/ml), the HBsAg level could range from 1.57 to 3.85 log IU/ml [14]. In another case series, the range of the HBsAg level among 46 HBeAg-negative patients with elevated ALT varied from −0.42 to 4.09 log IU/ml [8]. The relative lack of relationship between HBsAg level and disease activity might reflect an uncoupling of HBV DNA and HBsAg production in the HBeAg-negative phase. In line with natural history studies, a reduction in HBsAg is probably reflecting a stepping up of immune clearance [8], which is a logical predictor of response to peginterferon therapy in HBeAg-negative patients.

In a multicenter European study among 107 HBeAg-negative patients, the absence of an HBsAg decline together with an HBV DNA decline of <2 log at week 12 could predict the nonresponse to peginterferon with a 100 % negative predictive value, and this was suggested to be a stopping rule [15]. This European study composed of predominantly genotype D HBV infected patients, and this stopping rule has been externally validated by two other cohorts of predominantly genotype D HBV infected patients [16]. Whether the same rule holds true for patients infected with other HBV genotypes requires future studies to validate. In the current study by Marcellin et al. [11], as there were only 58 patients who received peginterferon monotherapy while the remaining patients had lamivudine combination, the small sample size rendered it difficult to assess the role of on-treatment HBV DNA as a predictor of response to peginterferon. With an HBsAg reduction of <10 % at week 24, 13.2 % patients could still achieve HBV DNA level of ≤2,000 IU/ml and 3.8 % patients could clear HBsAg at 5-year post-treatment. Therefore, a reduction of HBsAg by <10 % on-treatment is not a good stopping rule for peginterferon in HBeAg-negative patients.

In summary, Marcellin et al. have defined serum HBsAg level as an on-treatment predictor of the sustained response to peginterferon in HBeAg-negative patients. Although a ≥10 % reduction in HBsAg on-treatment can predict a long-term post-treatment response, it is insufficient to guide the regime of the peginterferon therapy. Future research should focus on how to integrate serum HBsAg into the currently available markers to improve patient selection and guide the treatment for peginterferon therapy in HBeAg-negative patients.

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