Sequential Combination Therapy with Pegylated Interferon Leads to Loss of Hepatitis B Surface Antigen and Hepatitis B e Antigen (HBeAg) Seroconversion in HBeAg-Positive Chronic Hepatitis B Patients Receiving Long-Term Entecavir Treatment

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Nucleos(t)ide analogues rarely result in a durable off-treatment response in chronic hepatitis B infection, whereas pegylated interferon (Peg-IFN) induces a long-lasting response only in a subset of patients. We assessed the effect of sequential combination therapy with Peg-IFN-α2a and entecavir in hepatitis B e antigen (HBeAg)-positive patients with prior long-term entecavir therapy and investigated the predictors of response to treatment. HBeAg-positive individuals who did not achieve HBeAg seroconversion during previous long-term entecavir therapy, receiving Peg-IFN-α2a added to ongoing entecavir therapy (sequential combination [S-C] therapy; n = 81) for 48 weeks or remaining on entecavir monotherapy (n = 116), were retrospectively included. A matched pair was created at a 1:1 ratio from each treatment group. The primary endpoint was HBeAg seroconversion at week 48. Subgroup analysis of response prediction was conducted for 81 patients with S-C therapy. More patients in the S-C therapy group achieved HBeAg seroconversion than those in the entecavir group (44% versus 6%; P < 0.0001). An HBeAg level of < 200 signal-to-cutoff ratio (S/CO) at baseline was a strong predictor for higher HBeAg seroconversion than that achieved when HBeAg was ≥200 S/CO (64.2% versus 17.9%; P < 0.0001). HBeAg level at baseline and the decrease in HBsAg levels predicted HBeAg loss in the S-C therapy group. The combination of baseline HBeAg of < 200 S/CO and HBsAg of < 1,000 IU/ml and an HBsAg decline at week 12 of ≥0.5 log₁₀ IU/ml provided the highest rate of HBeAg seroconversion (92.31%) and HBsAg loss (83.3%) at week 48. Patients receiving sequential combination therapy have a higher rate of HBeAg seroconversion and are more likely to experience HBsAg clearance than do those continuing entecavir monotherapy. Sequential combination therapy can be guided by baseline HBsAg/HBeAg levels and on-treatment HBsAg dynamics.

Hepatitis B virus (HBV) infection is endemic in Asia, the Pacific islands, Africa, Southern Europe, and Latin America, and chronic hepatitis B (CHB) is a global health threat. There are approximately 350 million chronic HBV surface antigen (HBsAg) carriers worldwide (1). Patients with CHB have an increased risk of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC), which results in about 1 million deaths per year (2). Antiviral treatment is effective in halting progression of CHB in many patients. Two classes of antiviral agents are available: nucleos(t)ide analogues (NUCs), such as entecavir (ETV), which inhibit the viral polymerase and interfere with viral replication, and interferon alpha (IFN-α), including conventional and pegylated forms, which has antiviral and immunomodulatory effects (3). NUCs are effective in most patients but must be continued indefinitely in the patients that do not achieve hepatitis B e antigen (HBeAg) seroconversion. In contrast, a finite course of pegylated IFN-α (Peg-IFN-α) can induce a long-lasting therapeutic response, but only in a subset of patients. Thus, novel strategies that induce durable responses in a larger proportion of patients after a finite course of treatment are required.

The combination of Peg-IFN-α and the earlier NUCs such as lamivudine is no more effective than Peg-IFN-α monotherapy in treatment-naïve patients (4, 5); thus, combination therapy is not recommended in current treatment guidelines (2, 6).

However, some recent studies have demonstrated that long-term NUC monotherapy can restore HBV-specific T-cell responsiveness (7), which may address a limitation of Peg-IFN-α therapy (8). Thimme and Dandri (9) argue that the addition of Peg-IFN-α to ongoing NUC therapy after restoration of HBV-specific T-cell responsiveness may be an effective strategy. They question whether previous studies of combined Peg-IFN-α/NUC therapy were ineffective because of the use of a NUC with
low potency (lamivudine) or of an otherwise inadequate regimen (e.g., premature initiation of combination therapy or limited duration of combination therapy).

In the present study, we investigated the efficacy of adding Peg-IFN-α2a to ongoing ETV in HBeAg-positive patients having received long-term (more than 2 years) ETV therapy (sequential combination [S-C] therapy). In addition, we investigated the baseline and on-treatment factors associated with treatment responses.

MATERIALS AND METHODS

Study population. This was a retrospective study of HBeAg-positive individuals, who did not achieve HBeAg seroconversion during previous long-term ETV therapy (≥2 years), receiving Peg-IFN-α2a added to ongoing ETV therapy (S-C therapy) or remaining on entecavir (ETV monotherapy) between May 2005 and August 2014 in the three participating centers in China. The study compared efficacy between S-C therapy and ETV monotherapy. Prior to the initiation of ETV therapy, all patients were confirmed to have been HBsAg positive for more than 6 months. Patients were required to have quantitative HBsAg and HBeAg levels documented at baseline and at weeks 12, 24, and 48 (end of treatment). Exclusion criteria included coexisting serious medical or psychiatric illness, cytopenia, decompensated liver disease, coinfection with hepatitis C or D virus or human immunodeficiency virus, and/or a history of drug or alcohol abuse. A total of 197 patients were enrolled. Among them, 81 received S-C therapy for 48 weeks after ≥2 years of ETV and 116 continued ETV monotherapy. Patients treated with S-C therapy stopped Peg-IFN-α2a but remained on ETV therapy after 48 weeks of combination treatment. For these patients who continued ETV monotherapy, the baseline time point was defined as 48 weeks prior to the latest visit at clinic.

Ethics. Informed consent was obtained from each patient included in the study. All procedures in this study are in accordance with the ethical standards of the responsible committee on human experimentation and conform to the principles of the Declaration of Helsinki.

Definition of treatment responses. The primary endpoint was HBeAg seroconversion (HBeAg loss accompanied by emergence of anti-HBe) at the end of treatment (week 48). HBsAg loss was a secondary endpoint.

Laboratory assays. HBeAg, anti-HBe antibodies, and anti-HBs antibodies in serum were measured by enzyme-linked immunosorbent assay (ELISA; Architect i2000sr; Abbott Laboratories, Chicago, IL, USA). HBV DNA levels in serum were determined by real-time PCR assay (ABI Prism 7300, real-time PCR system; lower detection limit, 1,000 IU/ml; PEC-Fluorescence Probing, USA). Serum HBsAg levels were determined by Elecsys HBsAg II assay (Roche Diagnostics GmbH, Mannheim, Germany; linear range, 0.05 to 52,000 IU/ml).

Table 1. Baseline characteristics of matched pairs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>S-C therapy (n = 50)</th>
<th>ETV monotherapy (n = 50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>31 (62%)</td>
<td>31 (62%)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>31.5 (23–54)</td>
<td>33 (23–53)</td>
<td>0.1629</td>
</tr>
<tr>
<td>Previous ETV duration (yr)</td>
<td>3 (2–5)</td>
<td>2 (2–4)</td>
<td>0.2214</td>
</tr>
<tr>
<td>HBV DNA (log IU/ml)</td>
<td>&lt;3 (&lt;3–3.9)</td>
<td>&lt;3 (&lt;3–6.5)</td>
<td>0.8078</td>
</tr>
<tr>
<td>HBsAg (log IU/ml)</td>
<td>3.6 (2.8–4.5)</td>
<td>3.8 (2.9–4.0)</td>
<td>0.8696</td>
</tr>
<tr>
<td>HBeAg (S/CO)</td>
<td>2.0 (0.05–3.2)</td>
<td>2.1 (1.0–3.3)</td>
<td>0.5822</td>
</tr>
<tr>
<td>ALT (U/liter)</td>
<td>31.5 (11–149)</td>
<td>24.5 (10–174)</td>
<td>0.1693</td>
</tr>
<tr>
<td>AST (U/liter)</td>
<td>39.5 (14–265)</td>
<td>27 (16–189)</td>
<td>0.0257</td>
</tr>
</tbody>
</table>

Table 1. Baseline characteristics of matched pairs

4 Patients were matched at a 1:1 ratio from each treatment group according to the following criteria: age difference of ≤5 years, gender, and baseline HBsAg level of ≤0.5 log_{10} IU/ml. Abbreviations: S-C, sequential combination; ETV, entecavir; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; AST, aspartic transaminase.

RESULTS

Baseline characteristics. A total of 197 HBeAg-positive patients with at least 2 years of prior entecavir exposure without HBeAg loss or seroconversion were included. Among them, 81 received S-C therapy and 116 continued ETV monotherapy. Patients were assigned to matched pairs at a 1:1 ratio in terms of age, gender, and baseline HBsAg level. The matched-pair set consisted of 50 patients treated with S-C therapy and 50 patients treated with ETV monotherapy. The two treatment groups were well balanced at baseline except for serum aspartic transaminase (AST) level (Table 1).

Response rates. After 48 weeks of treatment, significantly more patients in the S-C therapy group (22/50, 44%) achieved the primary endpoint of HBeAg seroconversion than those in the ETV monotherapy group (3/50, 6%; P < 0.001) (Fig. 1A). HBsAg loss at week 48 occurred only in two patients (2/50, 4%) treated with S-C therapy but was not achieved in patients treated with ETV monotherapy (P = 0.4949) (Fig. 1A). The P value for the comparison between the two groups did not reach statistical significance because of the small sample sizes.

On-treatment HBeAg and HBsAg decline according to treatment regimen. On-treatment HBeAg decline varied significantly by treatment regimen. Median serum HBeAg decreased in the S-C therapy group but remained stable in the ETV monotherapy group. The median changes in HBeAg levels from baseline were significantly greater in the S-C group than in the ETV monotherapy group at all postbaseline time points (Fig. 1B). Similar patterns were observed for the decline of HBsAg levels (Fig. 1C).

Patients treated with S-C therapy. The matched-pair analysis showed a significantly higher response rate of HBeAg seroconversion at week 48 in the S-C therapy group than in the ETV monotherapy group (44% versus 6%, P < 0.0001). We further investigated baseline and on-treatment factors associated with treatment responses in patients treated with S-C therapy. A total of 81 patients in our study were treated with S-C therapy. There were 39 episodes (48.1%) of HBeAg seroconversion at the end of treatment and 9 episodes (11.1%) of HBsAg loss.
Baseline factors associated with treatment responses. Univariate analysis showed that patients with HBeAg seroconversion were older at the initiation of S-C therapy (38 years versus 32 years, \( P < 0.0128 \)) and had lower baseline levels of HBeAg (19.7 versus 361.9 signal-to-cutoff ratio [S/CO], \( P = 0.001 \)), HBsAg (3.1 versus 3.8 log IU/ml, \( P = 0.001 \)), and alanine aminotransferase (ALT) (26 versus 37 U/ml, \( P = 0.0155 \)) (see Table S1 in the supplemental material). By multivariate analysis, lower baseline HBeAg levels were independently associated with achievement of HBeAg seroconversion after adjustment for gender, age, and baseline level of HBV DNA, HBsAg, and ALT (odds ratio [OR], 0.366 per 1 log HBsAg increase; 95% confidence interval [CI], 0.197 to 0.680; \( P = 0.001 \)) (see Table S2 in the supplemental material). ROC analysis identified the baseline HBeAg level as a predictive factor for HBsAg loss (AUC, 0.825, 95% CI, 0.684 to 0.966, \( P = 0.001 \)) (Fig. 2B).

Correlation between on-treatment HBsAg decline and treatment response in patients treated with S-C therapy. Among patients treated with S-C therapy, the decrease in HBsAg did not differ between patients with HBeAg seroconversion at week 48 and those who had no seroconversion (Fig. 3A). The median decline from baseline was 1.08 log IU/ml for responders and 0.87 log IU/ml for nonresponders at week 48 (\( P = 0.2245 \)). However, HBsAg levels decreased significantly more in patients who achieved HBsAg loss at week 48 than in those who did not throughout the treatment period (Fig. 3B). The median decline from baseline was 1.88 log IU/ml for responders and 0.88 log IU/ml for nonresponders (\( P = 0.0007 \)) at week 48. ROC analysis confirmed that HBsAg decline at week 12 or week 24 was significantly associated with response to S-C therapy (Fig. 3C). The AUCs were 0.825 (95% CI, 0.684 to 0.966) at week 12 and 0.832 (95% CI, 0.709 to 0.955) at week 24 for prediction of HBsAg loss.

Prediction of response. The performance of baseline and on-treatment variables in predicting responses to S-C therapy is shown in Table 2. A baseline HBeAg level of <200 S/CO was associated with a higher rate of HBeAg seroconversion at week 48 than a baseline HBeAg level of \( \geq 200 \) S/CO (34/53, 64.2% versus 5/28, 17.9%; \( P = 0.0001 \)) (Fig. 4A and C). HBsAg loss was achieved in 31.8% (7/22) of patients with a baseline HBsAg level of \( \geq 1,000 \) IU/ml compared with 3.4% (2/59) patients with higher HBsAg level (\( P = 0.0012 \)) (Fig. 4B and C). Rates of HBsAg loss were also significantly higher in those who achieved a \( \geq 0.5\) log reduction in the HBsAg level at week 12 (7/19, 36.8% versus 2/62, 3.2%; \( P = 0.004 \)) (Fig. 4D) than in those who did not. The combination of a baseline HBeAg level of <200 S/CO or HBsAg of <1,000 IU/ml plus HBsAg decline at week 12 of \( \geq 0.5\) log reduction provided the highest prediction of treatment response.
rate of HBeAg seroconversion (12/13, 92.31%)/HBsAg loss (5/6, 83.3%) at week 48.

Response rate 24 weeks after combination therapy. After 48 weeks of S-C therapy, all 81 patients stopped Peg-IFN-α/2a but remained on ETV monotherapy. The rates of HBeAg seroconversion and HBsAg loss both increased 24 weeks after return to ETV monotherapy (week 72). Significantly more patients achieved HBeAg seroconversion at week 72 than at week 48 (64.2% versus 48.1%, \( P < 0.0064 \); see Fig. S1 in the supplemental material). Although the \( P \) value for the comparison of HBsAg loss rate was not statistically significant, the trend was toward a higher rate of HBsAg loss at week 72 than at week 48 (18.5% versus 11.2%, \( P = 0.2686 \); see Fig. S1 in the supplemental material).

DISCUSSION

NUCs, such as ETV, are currently widely used in patients for the pronounced suppression of HBV DNA replication, safety profile, and oral administration. However, the indefinite treatment duration imposes a significant financial burden and a risk of drug-resistant mutants, which led to drawbacks to NUC administration. NUCs suppress viral replication by inhibiting HBV polymerase. Long-term NUC therapy results in high virological response rates but low serological response rates (10, 11). However, a recent analysis estimated that approximately 52 years of continuous NUC therapy would be needed to clear HBsAg, indicating that lifetime therapy would be required in most CHB patients (12). Thus, HBsAg loss, which is considered to be the definitive treatment endpoint for CHB, is rarely observed during NUC monotherapy. Peg-IFN induces a sustained response after a finite treatment, but the poor tolerance prohibits widespread use (13).

Accumulating evidence suggested that long-term NUC therapy enhances and complements the immunomodulatory effects of IFN in CHB patients, while IFN may inhibit formation of HBV protein and deplete the intrahepatic covalently closed circular DNA (cccDNA) pool (7, 8). Therefore, the optimization of combining IFN (Peg-IFN-α2a) and NUCs, such as ETV, may lead to the complete eradication of HBV. Early studies reported the efficacy of de novo or sequential combination of interferon and NUCs, which failed to show a benefit for this approach (4, 5, 14). A recent study reported the efficacy of switching to a finite course of Peg-IFN-α2a in patients on long-term ETV who have not experienced HBeAg seroconversion despite sustained HBV suppression (15). The result showed that patients who switched to Peg-IFN-α2a achieved higher HBeAg seroconversion at week 48 than those who continued ETV (14.9% versus 6.1%; \( P = 0.0467 \)) and only patients receiving Peg-IFN-α2a achieved HBsAg loss (8.5%). The study indicated a possibility to enhance the chances of HBeAg seroconversion by switching to a finite Peg-IFN-α2a therapy. Nevertheless, there has been debate on whether S-C therapy with Peg-IFN is better than “switch-to” Peg-IFN in patients with prior long-time exposure to NUCs (16).

In this study, ETV-experienced patients benefit more from a finite combination Peg-IFN-α2a/ETV therapy (S-C therapy) than...
from continuing ETV monotherapy. The rate of HBeAg seroconversion in the S-C therapy group was 44% compared with a modest 6% in the ETV monotherapy group. Moreover, two patients in the S-C therapy group achieved HBsAg loss compared with no patients in the continuous-monotherapy group. On the basis of our study, sequential combination of ETV and Peg-IFN-α2a appears to be a more promising alternative (in selected patients) to continuous ETV therapy or switch therapy (16). S-C therapy has shown to lead to a high rate of response in some small-cohort studies (17, 18). Further evidence in support of this strategy is provided by a recent randomized controlled trial in which Peg-IFN was added on after a 24-week ETV monotherapy (19). The result suggested that 24 weeks of Peg-IFN add-on therapy led to a higher proportion of HBeAg response than ETV monotherapy. Moreover, adding on Peg-IFN to ETV resulted in a greater off-treatment response after discontinuation of ETV. However, prior ETV exposure duration was only 24 weeks. A shorter duration of treatment may limit the serological response. Nevertheless, the above results suggested that, in order to be able to stop entecavir (or nucleos[t]ide analogue treatment), immune control is needed, and this study has shown that this may be achieved with nucleos(t)ide analogue-based Peg-interferon add-on. The mechanisms underlying the enhanced efficacy of S-C therapy and the duration of NUC therapy required to achieve an optimal response remain to be determined and should be addressed in future prospective randomized studies.

The selection of patients with prior ETV exposure who would benefit from sequential combination therapy was clinically valuable. Our investigation of factors associated with treatment responses showed that both baseline HBeAg/HBsAg levels and the

![FIG 3](image-url)

**FIG 3** Evaluation of on-treatment HBsAg decline for prediction of treatment response in 81 patients treated with S-C therapy. Median declines of HBsAg level during 48-week S-C therapy according to response of HBeAg seroconversion (A) or HBsAg loss (B). The data represent the medians for 81 patients in S-C therapy. (C) Receiver operating characteristic curve of HBsAg declines at week 12 and week 24 for the prediction of HBsAg loss.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Baseline and on-treatment prediction of treatment responses in the 81 patients with S-C therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment response and characteristics</td>
<td>No. (%) with response</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td></td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>39</td>
</tr>
<tr>
<td>Baseline HBeAg &lt;200 S/CO</td>
<td>34 (87.18)</td>
</tr>
<tr>
<td>Baseline HBsAg &lt;1,000 IU/ml</td>
<td>15 (38.46)</td>
</tr>
<tr>
<td>Baseline HBeAg &lt;200 S/CO + HBsAg decline ≥0.5 log at week 12</td>
<td>12 (30.77)</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td></td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>9</td>
</tr>
<tr>
<td>Baseline HBsAg &lt;1,000 IU/ml</td>
<td>7 (77.78)</td>
</tr>
<tr>
<td>HBsAg decline ≥0.5 log at week 12</td>
<td>7 (77.78)</td>
</tr>
<tr>
<td>Baseline HBsAg &lt;1,000 IU/ml + HBsAg decline ≥0.5 log at week 12</td>
<td>5 (55.56)</td>
</tr>
</tbody>
</table>

*PPV, positive predictive value; NPV, negative predictive value.*
decrease in HBsAg levels at weeks 12 and 24 of combination therapy are significantly associated with treatment responses. A serum HBsAg level of <1,000 IU/ml is considered to be indicative of good immune control status in CHB patients infected with certain HBV genotypes (20). In a recent study, the authors observed two distinct patterns of HBsAg decline in patients during 3 years of tenofovir treatment (21). In patients with a baseline HBsAg level of <1,000 IU/ml, the decline in HBsAg was significantly slower during tenofovir therapy, which might account for the rarity of HBsAg seroclearance. Similarly, a recent study found that a baseline HBsAg level of <1,000 IU/ml was the optimal cutoff level for predicting HBsAg seroclearance in patients treated with lamivudine for 10 years; nonetheless, only seven (10%) patients experienced HBsAg clearance in this study (22). Taken together, these data suggest that HBsAg-positive patients with HBsAg levels of <1,000 IU/ml during long-term NUC therapy may be entering the late stage of the “immune clearance phase” of CHB and are suitable candidates for sequential Peg-IFN-α2a/ETV combination therapy. In our study, HBsAg loss was achieved in 31.8% (7/22) of patients with baseline HBsAg levels of <1,000 IU/ml compared with 3.4% (2/59) patients with higher HBsAg levels (P = 0.0012). A similar pattern was observed in patients with baseline HBsAg levels of <200 S/CO who achieved a higher rate of HBeAg seroconversion (64.2% versus 17.9%, P < 0.0001). However, the baseline HBsAg level provided a positive predictive value (PPV) of only 31.8% for HBsAg loss, while the baseline HBeAg level had a PPV of 64.2% for HBeAg seroconversion. Therefore, the baseline factor alone cannot provide sufficient information for identifying patients who may benefit from sequential combination therapy. On-treatment factors should be taken into consideration.

Increasing evidence suggests that HBsAg levels at weeks 12 and 24 of treatment with Peg-IFN-α are important in predicting treatment response (23, 24). The results of a large multicenter study in treatment-naïve HBeAg-positive patients suggest that week 12 stopping rules should be based on the HBV genotype and that all patients with HBsAg levels of >20,000 IU/ml at 24 weeks should stop Peg-IFN-α therapy (25). Declines in HBsAg at weeks 12 and 24 of combination therapy were strong predictors of treatment response in our study. In our study, a significantly higher rate of HBsAg loss was achieved in patients with a decline in HBsAg levels of ≥0.5 log10 IU/ml at week 12 (36.8% versus 3.2%, P = 0.004).
Sequential Combination Therapy of ETV and Peg-IFN

However, an HBeAg decline at week 12 of $\geq 0.5 \log_{10} \text{IU/ml}$ still offered an unsatisfactory PPV of 36.8% for HBsAg loss. The combination of baseline and on-treatment factors increased the PPV to 92.3% for HBeAg seroconversion (baseline HBeAg, $<200 \text{ S/CO}$, plus HBsAg decline at week 12, $\geq 0.5 \log_{10} \text{IU/ml}$) and 83.3% for HBsAg loss (baseline HBsAg, $<1,000 \text{ IU/ml}$, plus HBsAg decline at week 12, $\geq 0.5 \log_{10} \text{IU/ml}$).

This study has certain limitations, the most important of which is the retrospective study design. This increases the probability that assignment to treatment was subject to selection bias. In order to control the variability of baseline parameters that may influence the response at the end of treatment between the two treatment groups, patients were matched at a 1:1 ratio according to the following criteria: age difference of $\leq 5$ years, gender, and baseline difference in HBsAg level of $\geq 0.5 \log_{10} \text{IU/ml}$. Second, the HBV genotype was not determined in this study, as most patients had achieved low HBV DNA levels ($<1,000 \text{ IU/ml}$) after previous long-term ETV therapy. Therefore, the impact of HBV genotype on the response to Peg-IFN was not observed. Third, only 81 patients received combination therapy. Moreover, subgroup analysis of response prediction was conducted in a limited number of patients. Only 12 patients with baseline HBeAg of $<200 \text{ S/CO}$ plus HBsAg decline of $\geq 0.5 \log$ at week 12 achieved HBeAg seroconversion, and 5 patients with baseline HBsAg of $<1,000 \text{ IU/ml}$ plus HBsAg decline of $\geq 0.5 \log$ at week 12 achieved HBsAg loss. Large, prospective studies are still required to confirm and extend the results of our study.

In conclusion, our study suggests that patients receiving ongoing long-term ETV therapy have a higher rate of HBeAg seroconversion and are more likely to experience HBsAg clearance by the addition of Peg-IFN-a2a (sequential combination therapy) than from continuing ETV monotherapy. Patients with a baseline HBsAg level of $<1,000 \text{ IU/ml}$ are excellent candidates for the addition of 48 weeks of Peg-IFN therapy. The decline in HBsAg during treatment should be taken into consideration to guide therapy decision. We suggest that sequential combination Peg-IFN-a2a/ETV therapy has a potential role in the treatment of HBeAg-positive patients with CHB.

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We declare that we have no conflicts of interest.

REFERENCES


