HBV DNA level at 24 weeks is the best predictor of virological response to adefovir add-on therapy in patients with lamivudine resistance

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Introduction

High-level HBV replication is a major risk factor for progression to end-stage complications such as decompensated cirrhosis and hepatocellular carcinoma (HCC) [1,2]. Therefore, the goals of therapy in patients with HBV are to limit or reverse disease progression by sustained suppression of HBV replication. Although extended lamivudine treatment can achieve a virological response [3], long-term lamivudine therapy is associated with progressively increasing rates of viral resistance because of mutations within the tyrosine–methionine–aspartate–aspartate (YMDD) motif of the HBV DNA polymerase [3,4]. The initial benefits of lamivudine are therefore lost over time among the patients that develop YMDD mutations, indicating a clear need for additional therapy in such patients [3,5].

Adefovir has been shown to potently suppress both wild-type and lamivudine-resistant HBV [6–9]. Early studies have shown that adding adefovir to lamivudine therapy or switching to adefovir can resuppress viral replication, normalize alanine aminotransferase (ALT) levels and provide significant histological improvement in patients that are lamivudine resistant [8,10]. However, a comparative study of adefovir monotherapy versus adefovir and lamivudine combination therapy showed that adding adefovir to ongoing lamivudine therapy was preferable to switching to adefovir monotherapy in terms of potent antiviral effects and a lower rate of resistance [11]. Current therapeutic guidelines therefore recommend adding adefovir to lamivudine treatment rather than switching to adefovir monotherapy.

Several studies have shown that a rapid virological response is associated with lower rates of antiviral drug resistance in patients with HBV [12–14]. Therefore, antiviral therapy should aim to suppress viral replication
as quickly and completely as possible. In addition, the patients that respond to nucleos(t)ide therapy should be identified at an early stage in order to adjust treatment and prevent future development of antiviral drug resistance. Many pre-treatment variables have been investigated to identify predictive factors that allow for the selection of patients who are most likely to respond to therapy [11,13,15–18]. Lampertico et al. [17] demonstrated that the addition of adefovir during the early stage of lamivudine resistance was significantly more effective in suppressing HBV DNA than was the delayed onset of combination therapy. Therefore, adefovir should be added to lamivudine as early as genotypic resistance is detected. Recently, HBV DNA levels during treatment have been found to be more useful than pre-treatment variables in predicting the outcome of antiviral treatment [14,17,19–21]. Patients with suboptimal responses to adefovir monotherapy in chronic hepatitis B (CHB) with lamivudine resistance are at increased risk of resistance development, suggesting that adefovir monotherapy almost inevitably leads to drug resistance if viral suppression is incomplete [22–24]. However, little data are available regarding information on the association between HBV DNA levels at various time points during lamivudine and adefovir combination treatment and the early prediction of a virological response in CHB patients with lamivudine resistance.

The aim of this study was to assess the baseline and on-treatment clinical and demographic variables to determine the factors predictive of a virological response to combination treatment. Using a standardized, quantitative PCR test to measure the HBV DNA levels at various time points during combination treatment, the optimal time for measurement during treatment was determined, as was the cut-off value of HBV DNA, for the prediction of virological responses in patients with lamivudine resistance. In addition, the long-term efficacy of lamivudine and adefovir combination therapy in CHB patients with lamivudine resistance was investigated.

Methods

Patients

A total of 183 patients with CHB and genotypic evidence of lamivudine-resistant HBV were treated with lamivudine and adefovir from August 2003 to April 2010. Among these 183 patients, 122 received lamivudine and adefovir combination therapy for >24 months. The remaining 61 patients were excluded from this study: 40 patients received combination therapy for <24 months, 10 patients had irregular treatment owing to poor compliance and 11 patients were lost to follow-up. Patients with impaired renal function (serum creatinine >1.5 mg/dl), antibodies to HCV or HIV, or autoimmune hepatitis were excluded. Additional criteria for exclusion were pregnancy, lactation and alcohol abuse (>40 g/day of ethanol). Diagnoses of chronic hepatitis and liver cirrhosis were made on the basis of liver biopsy features or, if these were unavailable, on clinical, laboratory and imaging data. Written informed consent was obtained from all patients participating in this study; the research was approved by the Institutional Review Board at the Ulsan University Hospital, Ulsan, Korea.

Laboratory measurements

Serum HBeAg, anti-HBe and HBV DNA levels were measured, and liver and kidney function tests were performed at weeks 4, 12, 24, 36 and 48 of treatment, and every 12 weeks thereafter. Serum was obtained during every follow-up visit and stored at -20°C. HBV DNA levels were quantified using the COBAS TaqMan HBV test (Roche, Branchburg, NJ, USA), which has a lower detection limit of 12 IU/ml (60 copies/ml). Serum HBeAg and anti-HBe levels were measured by microparticle enzyme immunoassay (AxSYM; Abbott, Chicago, IL, USA). Genotypic resistance to adefovir was looked for at 24-week intervals in all HBV DNA-positive serum samples, and was tested by direct viral genome sequencing [17]. Patients underwent surveillance for HCC every 24 weeks; repeated abdominal ultrasounds and serum α-fetoprotein measurements were performed.

Definitions

The primary outcome measure was the virological response at week 96 of combination treatment. Secondary outcomes included HBeAg seroconversion, normalization of ALT levels and development of virological breakthrough or emergence of genotypic adefovir mutations. A virological response was defined as the absence of serum HBV DNA by PCR assay (<12 IU/ml) on two consecutive measurements within 96 weeks of treatment. HBeAg seroconversion was defined as the loss of HBeAg, accompanied by the detection of anti-HBe and the absence of serum HBV DNA. Virological breakthrough was defined as a >1 log_{10} IU/ml increase in the serum HBV DNA from the nadir on two consecutive measurements or in the last available measurement. Primary non-response was defined as an HBV DNA reduction of <1 log_{10} IU/ml from baseline within the first three months of treatment. Genotypic resistance to adefovir was defined as the emergence of adefovir resistance mutations (rtA181T/V and rtN236T).

Statistical analysis

Continuous variables were compared using the Student’s t-test and categorical variables were compared using the χ² test. The cumulative probability rates of clinical outcomes were calculated using the Kaplan–Meier method and the difference was determined by the log rank test.
To identify factors predictive of outcome among the pre-treatment and on-treatment variables, the variables for clinical outcomes using the $\chi^2$ test or univariate logistic regression were compared. Multivariate analysis was carried out using a stepwise logistic regression model.

To determine the cutoff levels of HBV DNA for prediction of clinical outcomes at weeks 0, 4, 12, 24, 36 and 48 during combination treatment, the odds ratios (ORs) and receiver operating characteristics (ROCs) were evaluated with the overall accuracy assessed by the area under the curve (AUROC). For balanced optimization of both sensitivity and specificity, using a decision-theoretic approach, thresholds were observed by maximizing the sensitivity and specificity. The AUROCs and their 95% CIs were measured to assess the degree of discrimination provided by these variables. Sensitivity, specificity, positive predictive value and negative predictive value were calculated. The highest $\chi^2$ test identified the optimal cutoff point. All data were analysed using the statistical package SPSS for Windows (version 17.0; SPSS Inc., Chicago, IL, USA). In all cases, a two-tailed $P$-value of $<$0.05 was considered statistically significant.

**Results**

**Demographics**

Demographics, baseline and on-treatment characteristics for the whole group of patients ($n=122$) and patients with a virological response ($n=62$) and without a virological response ($n=60$) at week 96 of treatment are summarized in Table 1. The median duration of lamivudine and adefovir combination therapy was 32 months (range 24–78). Forty-six (33.7%) patients were treated with combination treatment for $>$36 months. Sixteen (13.1%) patients had normal ALT, 15 (12.3%) had ALT $<2\times$ the upper limit of normal (ULN), 38 (47.5%) had ALT 2–5×ULN, 21 (17.2%) had ALT 5–10×ULN and 12 (9.8%) patients had ALT $>$10×ULN. Seven (2.8%) patients had a serum bilirubin $>$3×ULN. There were no differences in the baseline parameters between the two groups of patients, except that those with a virological response had significantly lower baseline mean HBV DNA levels.

**Clinical outcomes after lamivudine and adefovir combination treatment**

The mean reductions in HBV DNA at weeks 4, 12, 24, 36, 48 and 96 were 2.24 log $10$ IU/ml (range $-0.13$–$5.34$), $2.92$ ($-0.47$–$6.82$), $3.43$ ($-0.46$–$7.04$), $3.64$ ($-0.62$–$7.04$), $3.79$ ($-0.28$–$7.04$) and $3.94$ ($0.89$–$7.04$), respectively. Thirteen patients (10.7%) were primary non-responders. The rates of virological response at 12, 24, 36 and 48 weeks were 23.8% (29/122), 35.3% (43/122), 42.6% (52/122) and 43.4% (53/122), respectively (Figure 1). At 96 weeks of lamivudine and adefovir combination therapy, the HBV DNA level was undetectable in 62 patients (50.8%), 12–200 IU/ml in 17 patients (13.9%), 200–2,000 IU/ml in 16 patients (13.1%), 2,000–20,000 IU/ml in 10 patients (8.2%) and $>$20,000 IU/ml in 17 patients (13.9%). Among 106 patients with abnormal ALT levels at baseline, normalization of ALT levels was achieved in 75.5% (80/106) and 82.1% (87/106) of patients at 48 and 96 weeks of combination treatment, respectively. Among 94 HBeAg-positive patients, 13 (13.8%) patients achieved HBeAg seroconversion within 96 weeks of combination treatment. The HBeAg seroconversion rates at 24, 48 and 96 weeks were 10.6% (10/94), 12.8% (12/94) and 13.8% (13/94), respectively. Virological breakthrough was observed in only one (0.8%) patient at 84 weeks during combination treatment. Genotypic resistance to adefovir was looked for in all patients at baseline and in patients with persistent viremia ($>$200 IU/ml) at 24-week intervals by direct sequencing analysis while on treatment. Two patients had the rtA181T mutation at baseline. De novo genotypic adefovir
mutations occurred in 18 (15.0%) patients at a median of 48 weeks (range 24–96). Adefovir resistant substitutions were detected in 7 (5.8%) patients (rtA181T in 5 and rtN236T in 2) at 48 weeks of combination treatment. Within 96 weeks of treatment, adefovir mutations were detected in 18 (15.0%) patients at a median of 48 weeks (range 24–96). Adefovir resistant substitutions were detected in 7 (5.8%) patients (rtA181T in 5 and rtN236T in 2) at 48 weeks of combination treatment. Within 96 weeks of treatment, adefovir mutations were detected in 18 (15.0%) patients (rtA181T in 14, rtA181V in 1 and rtN236T in 3). The mutation profile at 96 weeks of treatment showed that 5 patients (rtA181T in 2, rtA181V in 1, and rtN236T in 2) rapidly cleared HBV DNA, whereas adefovir-resistant mutations (rtA181T in 12 and rtN236T in 1) were persistently detected in the remaining 13 patients.

Serum creatinine levels ≥0.5 mg/dl above baseline were observed in only two (1.6%) patients at 72 and 128 weeks after combination treatment. Dose reductions (10 mg every other day) resulted in improvements in the serum creatinine level. Five (4.1%) patients developed HCC during a median follow-up of 84 weeks (range 32–168 weeks).

### Baseline and on-treatment factors and their relationship to subsequent virological response at week 96 of treatment

We sought to determine the impact on virological response of baseline demographic and clinical factors. We also analysed the predictive values of the absolute HBV DNA levels and the reduction of HBV DNA levels from baseline measured at various time points during treatment. Univariate analysis revealed that pre-treatment HBV DNA levels; absolute HBV DNA levels at weeks 4, 12, 24, 36 and 48; and reduction of HBV DNA levels at weeks 4, 12, 24, 36 and 48 were significantly related to virological response to 96-week treatment (Table 2). In multivariate analysis, the absolute HBV DNA level at week 24 (OR 0.150; 95% CI 0.051, 0.440; \( P < 0.001 \)), 48 (OR 0.223; 95% CI 0.064, 0.853; \( P = 0.028 \)) and pre-treatment HBV DNA levels (OR 0.613; 95% CI 0.456, 0.824; \( P = 0.001 \)) were significantly related to virological response to 96-week treatment (Table 2).

### HBV DNA levels over time and their relationship to subsequent virological response at week 96 of treatment

To determine whether there was a best measurement time for and an optimal cutoff level of HBV DNA levels over time and their relationship to subsequent virological response at week 96 of treatment

**Table 2. Univariate and multivariate analysis of baseline and on-treatment characteristics predicting virological response at week 96 of treatment**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with VR ((n=62))</th>
<th>Patients without VR ((n=60))</th>
<th>Univariate (P)-values</th>
<th>Multivariate (P)-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HBV DNA level</td>
<td>5.32 ±1.76</td>
<td>6.94 ±1.21</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>On-treatment characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA level at week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3.25 ±1.61</td>
<td>5.10 ±0.82</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1.92 ±1.04</td>
<td>4.51 ±1.10</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>1.35 ±0.65</td>
<td>4.07 ±1.15</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>36</td>
<td>1.20 ±0.44</td>
<td>3.77 ±1.24</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>1.16 ±0.38</td>
<td>3.51 ±1.26</td>
<td>&lt;0.001</td>
<td>0.028</td>
</tr>
<tr>
<td>Reduction of HBV DNA levels from baseline to week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.29 ±1.44</td>
<td>2.20 ±0.99</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>3.40 ±1.54</td>
<td>2.44 ±1.38</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>3.97 ±1.68</td>
<td>2.87 ±1.42</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>4.10 ±1.79</td>
<td>3.17 ±1.57</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>4.15 ±1.79</td>
<td>3.41 ±1.61</td>
<td>0.019</td>
<td></td>
</tr>
</tbody>
</table>

Continuous variables are expressed as means ± standard deviations. VR, virological response
predicted virological response, the HBV DNA levels were measured at various time points (baseline, 4, 12, 24, 36 and 48 weeks) during lamivudine and adefovir combination treatment. AUROCs, designed to aid in the prediction of the virological response, were derived from pre-treatment and on-treatment HBV DNA levels during treatment. The exact values of AUROCs at each time point, from baseline to week 48, are listed in Table 3 and illustrated in Figure 2. The best time for measurement (highest AUROCs) of the HBV DNA level for the prediction of the virological response at week 96 was at 24 weeks (AUROC 0.978; 95% CI 0.949, 1.000; \( P < 0.001 \)). HBV DNA levels at week 24 had a greater power to predict the virological response at week 96 than did pre-treatment HBV DNA levels (AUROC 0.771; 95% CI 0.640, 0.902; \( P < 0.001 \)).

Next, to determine whether an optimal cutoff level of HBV DNA at week 24 of treatment predicted the subsequent virological response at week 96, the HBV DNA cutoff values that provided maximal predictive efficacy were determined. The best cutoff value of the HBV DNA level for the prediction of the virological response at week 96 of treatment was 200 IU/ml (3 \( \log_{10} \) copies/ml), with a sensitivity and specificity of 90.3% and 95.0%. This HBV DNA level threshold yielded an OR of 18.07 (95% CI 5.98, 54.59), and a positive predictive value and negative predictive value of 94.9% and 90.5%, respectively. A virological response was achieved in 56 (94.9%) patients (\( n = 59 \)) with HBV DNA levels <200 IU/ml at week 24 (\( P < 0.001 \)). That is, 56 (90.3%) out of 62 patients that achieved a virological response at week 96 of treatment had <200 IU/ml HBV DNA.

To compare pre-treatment and on-treatment HBV DNA levels with the subsequent achievement of a virological response, the optimal cutoff level of the pre-treatment HBV DNA for the prediction of a virological response at week 96 of treatment was determined. According to the ROC curve analysis, the best cutoff value of the pre-treatment HBV DNA level for the prediction of a virological response at week 96 of treatment was 6.3 \( \log_{10} \) IU/ml (7 \( \log_{10} \) copies/ml) of HBV DNA, with a sensitivity and specificity of 66.1% and 76.7%. Using this cutoff value, of 55 patients who had <6.3 \( \log_{10} \) IU/ml of HBV DNA at baseline, 41 patients were subsequently found to have a virological response at week 96 of treatment. That is, 41 (66.1%) out of 62 patients that achieved a virological response at week 96 of treatment had <6.3 \( \log_{10} \) IU/ml of HBV DNA. Conversely, 33.9% of patients with a virological response had \( \geq 6.3 \log_{10} \) IU/ml of HBV DNA. Therefore, significantly more patients among those with HBV DNA levels <200 IU/ml at week 24 than patients with HBV DNA <6.3 \( \log_{10} \) IU/ml at baseline had achieved a virological response at week 96 of treatment (94.9% versus 66.1%; \( P < 0.001 \)).

### Table 3. Areas under ROC curves using HBV DNA levels at each time point of lamivudine and adefovir combination treatment to predict virological responses at 96 weeks

<table>
<thead>
<tr>
<th>Time</th>
<th>AUC</th>
<th>Standard error</th>
<th>( P )-values*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.771</td>
<td>0.670</td>
<td>0.001</td>
<td>0.640, 0.902</td>
</tr>
<tr>
<td>Week 4</td>
<td>0.878</td>
<td>0.049</td>
<td>&lt;0.001</td>
<td>0.782, 0.975</td>
</tr>
<tr>
<td>Week 12</td>
<td>0.937</td>
<td>0.029</td>
<td>&lt;0.001</td>
<td>0.880, 0.994</td>
</tr>
<tr>
<td>Week 24</td>
<td>0.978</td>
<td>0.015</td>
<td>&lt;0.001</td>
<td>0.949, 1.000</td>
</tr>
<tr>
<td>Week 36</td>
<td>0.966</td>
<td>0.023</td>
<td>&lt;0.001</td>
<td>0.920, 1.000</td>
</tr>
<tr>
<td>Week 48</td>
<td>0.962</td>
<td>0.025</td>
<td>&lt;0.001</td>
<td>0.913, 1.000</td>
</tr>
</tbody>
</table>

AUROCs, area under the curve; ROC, receiver operating characteristic. *Statistical significance implies that the corresponding AUC was significantly different from 0.5.

### Figure 2. ROC curves using HBV DNA levels at various time points during adefovir and lamivudine combination treatment to predict the virological response at week 96 of treatment.
Discussion

This is the first study of HBV DNA levels during lamivudine and adefovir combination therapy in lamivudine-resistant CHB that analysed the prediction of a virological response at 96 weeks of treatment. According to the analysis, on-treatment and pre-treatment HBV DNA levels were significantly related to the virological response to treatment. Furthermore, the HBV DNA levels at week 24 had a greater power to predict the virological response at week 96 than did pre-treatment HBV DNA levels. In addition, the best cutoff value for the HBV DNA level, at week 24, for the prediction of a virological response at week 96 was 200 IU/ml (3 log_{10} copies/ml).

For patients with lamivudine resistance, adefovir add-on therapy is effective at restoring viral suppression and preventing the emergence of resistance as shown in previous studies [8,11,15,17,25]. However, in this study, a virological response occurred in 43.3% and 50.8% at 48 and 96 weeks of combination therapy, respectively. Half of the patients still had detectable HBV DNA following 24 months of lamivudine and adefovir combination therapy in lamivudine-resistant CHB. These finding are consistent with previously reported studies [8,9,26] showing that the virological response rates at 1 year of treatment were 20–35% in highly vireamic patients who had 8–9 log_{10} copies/ml of HBV DNA, compared with 57% of patients with lower baseline viraemia. By contrast, Lampertico et al. [25] reported the long-term efficacy of combined adefovir and lamivudine therapy in patients with lamivudine-resistant hepatitis B. The 1-, 2-, 3-, and 4-year rates of virological response were 68%, 79%, 87% and 85%, respectively. The rate of virological response in this study was lower than the rates reported by Lampertico et al. [25]. In our study, de novo genotypic adefovir mutations occurred in 18 (15.0%) patients. The rtA181T and rtA181V mutations were detected in 14 patients and 1 patient, respectively. Three patients developed the rtN236T mutation during treatment, unlike the result of Lampertico et al. [22]. The rates of de novo genotypic adefovir mutations at 48 and 96 weeks were 7 (5.8%) and 18 (15.0%), respectively. Such a low virological response and high adefovir mutation rates in this study could be explained by the patient population that had relatively high levels of HBV DNA (median, 7.1 log_{10} copies/ml) at baseline compared with the patients reported by Lampertico et al. [25] (median, 6.0 log_{10} copies/ml), confirming the importance of baseline viraemia to the outcome of combination treatment. In addition, several previous studies have suggested that pre-treatment ALT levels, HBeAg positivity, female gender, HBV genotype and the lamivudine mutation pattern were associated with the virological response [11,13,16,18,27]. These additional factors might explain the lower virological response and higher detection rate of the adefovir mutations in the patients reported in this study compared with those in previous reports. In accordance with previous studies [22–24], the other possible explanation for suboptimal responses to combination therapy could be the relative low potency of the usual daily doses of adefovir and lamivudine in CHB patients with lamivudine resistance. Therefore, either the dose of adefovir should be increased or another drug that has a similar resistance profile but higher potency against lamivudine-resistant mutants should be substituted. Tenofovir fumarate, to which lamivudine-resistant HBV strains are also sensitive, is more potent than adefovir and would be an excellent candidate [28,29].

Earlier identification of likely efficacy outcomes could help reduce virological breakthrough and treatment costs in patients who are unlikely to achieve a virological response to antiviral treatment. Lampertico et al. [17] demonstrated that the addition of adefovir to ongoing lamivudine, during the early stage of lamivudine resistance, was significantly more effective in suppressing HBV DNA than was the delayed onset of combination therapy after HBV DNA increased to higher levels. That is, 2 years after instituting adefovir rescue therapy, the virological response was 100% in patients that were treated at the time of detection of genotypic resistance; however, only 78% presented with both genotypic and biochemical breakthrough. In this study, the week-96 virological response rate to combination treatment was 31.3% in the highly viremic CHB patients, with HBV DNA >6.3 log_{10} IU/ml (7 log_{10} copies/ml), compared with 80.5% for CHB patients with lower baseline viraemia (<6.3 log_{10} IU/ml of HBV DNA). This observation is consistent with the data reported recently by Lampertico et al. [17] and suggests that, to maximize the efficacy of treatment in patients with CHB selecting resistant strains to lamivudine, adefovir should be added to lamivudine as early as genotypic resistance is detected. Although such pre-treatment HBV DNA levels are clinically helpful, no single variable can accurately predict treatment responses. Among the 55 patients with <6.3 log_{10} IU/ml of HBV DNA at baseline, 41 patients showed complete virological response, which was only 66.1% of the total 62 patients with virological responses at week 96 of treatment. That is, if one were to discontinue therapy in all patients with more than 6.3 log_{10} IU/ml of HBV DNA at baseline, one would miss 34% of patients achieving a virological response at week 96 of treatment. Recently, HBV DNA levels during treatment have been reported to be more useful than pre-treatment HBV DNA levels in predicting the outcome of antiviral treatment [13,20,30–32]. This study also
showed that HBV DNA levels at week 24 of treatment performed better with respect to the prediction of virological responses at week 96 of treatment than pre-treatment HBV DNA levels. Using 200 IU/ml of HBV DNA at week 24, patients that had HBV DNA levels <200 IU/ml at week 24 had a 90.3% chance of achieving a virological response after 96 weeks of treatment. Conversely, patients with HBV DNA ≥200 IU/ml at week 24 had a low chance of achieving a virological response. The results of this study can help clinicians decide whether to continue combination therapy on the basis of an individual patient’s probability of a virological response.

This study had several important limitations. The study design is retrospective and observational including a heterogeneous patient population with a relatively short-term follow-up period. The PCR sequencing method used in our study almost certainly could not detect minor species comprising <30% of the entire HBV DNA population. It is thus possible that we underestimated the prevalence of genotypic adefovir-resistant mutations. Moreover, the HBV genotypes were not determined. However, nearly all cases of HBV in Korea have the C2 genotype [33]. Nevertheless, this study is the first to show that measurements of HBV DNA levels during lamivudine and adefovir combination treatment can be used to predict virological responses in CHB patients with lamivudine resistance. Although HBV DNA levels at baseline are often used to predict the antiviral potency of lamivudine and adefovir combination treatment in CHB patients with lamivudine resistance, the results of this study suggest that on-treatment HBV DNA levels are a better marker of therapeutic outcome.

In conclusion, HBV DNA levels measured at week 24 after lamivudine and adefovir combination treatment in CHB patients with lamivudine resistance provided a better prediction of virological responses than baseline HBV DNA levels. Patients with a low viral load at baseline were confirmed to have a good long-term response to combination treatment. Furthermore, if on-treatment HBV DNA levels are used combined with baseline HBV DNA levels, the application of both levels to guide therapy decisions might be beneficial.

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Disclosure statement

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