Original article

A 96-week randomized trial of switching to entecavir in chronic hepatitis B patients with a partial virological response to lamivudine

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Background: Growing numbers of chronic hepatitis B (CHB) patients in the Asia-Pacific region have failed first-line therapy with low genetic barrier drugs. This prospective, 96-week study investigated the antiviral efficacy, safety and tolerability of switching to entecavir versus maintaining lamivudine in CHB patients with a partial virological response to lamivudine.

Methods: A total of 72 hepatitis B e antigen (HBeAg)-positive patients, with serum HBV DNA ≥ 60 IU/ml after ≥6 months lamivudine monotherapy were randomized 1:1 to receive either entecavir 1.0 mg/day, or continued lamivudine 100 mg/day.

Results: Mean duration of prior lamivudine treatment was 15.1 months in the lamivudine-maintained patients and 16.1 months in the entecavir-switch patients, with mean baseline HBV DNA levels of 4.66 and 4.55 log10 IU/ml, respectively. A greater proportion of entecavir-switch than lamivudine-maintained patients achieved undetectable HBV DNA at all time points (67.6% versus 11.4% at week 96; P<0.001). Entecavir-switch patients achieved a greater mean decrease in HBV DNA level by week 4, maintained through week 96. Entecavir-switch patients with baseline HBV DNA <5 log10 IU/ml were more likely to achieve a virological response at week 96. A total of 6 (17.6%) entecavir-switch and 2 (5.7%) lamivudine-maintained patients achieved HBeAg loss, and 3 (8.8%) entecavir and 1 (2.9%) lamivudine patients achieved HBeAg seroconversion. Genotypic resistance to the assigned intervention emerged in 82.9% (29/35) of lamivudine-maintained patients, and in 3% (1/34) of entecavir-switch patients after 96 weeks.

Conclusions: Switching to entecavir in patients with a partial virological response to lamivudine resulted in increased virological efficacy and lower rates of antiviral resistance than maintaining lamivudine.

Introduction

Chronic hepatitis B (CHB) remains an important public health concern with an estimated 350 million patients worldwide, 75% of whom live in the Asia-Pacific region [1]. CHB in this region is typically acquired perinatally [2], which is associated with a higher risk of liver disease progression [3]. The prevalence of HBV infection in Korea has been reported to be 3.1% in males and 4.1% in females older than 10 years [4]. Furthermore, HBV genotypes B and C are highly prevalent in the Asia-Pacific region [5]. In Korea, HBV genotype C infections are nearly universal [6], known to be associated with severe disease and a high risk of developing hepatocellular carcinoma (HCC) [7–9]. Uncontrolled viral replication reflected by high serum HBV DNA level is a known risk factor for disease progression to cirrhosis and HCC [10]. The primary aim of antiviral therapy, therefore, is to permanently suppress HBV replication and prevent disease progression [11].
Antiviral therapy has been shown to reduce the risk of cirrhotic complications and improve clinical outcomes in patients with CHB [12]. Lamivudine (3TC) is a nucleoside analogue that has been shown to be efficacious with a favourable safety profile [13]; however, its long-term efficacy is limited by virological breakthrough due to the emergence of drug-resistant HBV mutations [14,15]. The reported emergence of mutations in the YMDD motif of the HBV polymerase gene is 24% after 1 year of 3TC therapy, rising to 70% after 4 years [15]. The development of resistance results in increased viral load and serum alanine transaminase (ALT), decreased rates of hepatitis B e antigen (HBeAg) seroconversion and blunting of histological improvement [13,16–21]. The emergence of resistance has also been shown to have a negative impact on future treatment options [22,23]. Despite this evidence, drugs with low genetic barriers to resistance, such as 3TC, have long been used as first-line therapy in Asia-Pacific countries, including Korea, primarily due to cost.

Global clinical practice guidelines have recognized the problems resulting from first-line therapy failure with low genetic barrier drugs and thus recommend using efficacious drugs with high genetic barriers to resistance, such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF) [22,24,25]. Effective screening of patients who have either a primary non-response or partial virological response (PVR) to first-line therapy may be beneficial in order to optimize therapy [24,26]. Early intervention is indicated for these patients before the emergence of antiviral resistance, which is known to limit future treatment options and is associated with worsening of disease [22]. European clinical practice guidelines recommend that patients who have a PVR at week 24 while receiving 3TC or telbivudine should switch to a more potent drug (ETV or TDF), or add on a more potent drug that does not share cross-resistance [24]. Although these recommendations are based on expert opinion and discussion of available scientific evidence, further data are required to support this strategy.

The avoidance of drug resistance is strongly emphasized in global treatment guidelines [11,22,24]. The aim of this study was to investigate the antiviral efficacy, safety and tolerability of a prompt switch to ETV versus maintaining 3TC in patients with a PVR to 3TC. The results may validate the rationale for switching to a more potent antiviral agent before the development of resistance.

Methods

Study design

This was a prospective randomized open-label 96-week Phase IV study evaluating the efficacy, safety and tolerability of continuing 3TC versus switching to ETV in HBeAg-positive CHB patients with detectable HBV DNA (≥60 IU/ml by PCR) while on 3TC for ≥6 months. Eligible patients were enrolled from 5 centres in Korea, and randomized 1:1 to receive either 1.0 mg ETV (BARACLUDE®, Bristol–Myers Squibb, Princeton, NJ, USA) or 100 mg 3TC (ZEFFIX®, GlaxoSmithKline, Middlesex, UK) orally, daily. Patients were randomized and allocated to treatment by a central investigator using a computer-generated number pre-assigned to a treatment arm.

In this study primary non-response was defined as <1 log10 IU/ml decrease in serum HBV DNA after 6 months antiviral treatment; virological breakthrough as ≥1 log10 IU/ml increase in serum HBV DNA above nadir on two occasions ≥1 month apart, while on treatment and after achieving initial response; and biochemical breakthrough as elevated ALT after achieving normalization and while on treatment. The upper limit of normal (ULN) for ALT was defined as 40 IU/l. Clinical breakthrough was defined as elevated ALT ≥2×ULN while on treatment plus virological breakthrough, and genotypic resistance as the presence of signature nucleotide mutations in the HBV polymerase gene previously demonstrated to be associated with antiviral resistance. Patients with clinical breakthrough or those who developed antiviral resistance were discontinued from the study, and transitioned to commercially available antiviral therapy (add-on adefovir in both study arms).

Patients

Patients were enrolled and treated between February 2008 and June 2011 at five centres in Korea: Yonsei University College of Medicine, Seoul; Pusan National University School of Medicine, Busan; Yeungnam University College of Medicine, Gyeongsan; Kyungpook National University College of Medicine, Daegu; and Korea University College of Medicine, Seoul. Patients eligible for entry to the study were aged ≥18 years with HBeAg-positive CHB being treated with 3TC for ≥6 months, and with HBV DNA ≥60 IU/ml. Eligible patients had ALT <10×ULN with no evidence of HCC. Patients were excluded from this study if they had been treated with other antiviral drugs in combination with 3TC, or had serological evidence of coinfection with HCV, HIV or hepatitis D virus. Those with decompensated liver disease, pregnant and breastfeeding women, and patients with evidence of M204V/I mutations in the YMDD motif at enrolment were also excluded.

Outcomes and analyses

The primary end point in this study was the proportion of patients with undetectable HBV DNA (<60 IU/ml by PCR assay) at week 96. Secondary end points included: the proportion of patients with undetectable HBV DNA at week 48; proportion developing
antiviral-resistance-conferring mutations at weeks 48 and 96; mean HBV DNA change from baseline at weeks 48 and 96; proportion of patients with ALT normalization, HBeAg loss, HBeAg seroconversion, hepatitis B surface antigen (HBsAg) loss and HBsAg seroconversion at weeks 48 and 96; cumulative discontinuation rate due to 3TC or ETV resistance mutations and clinical breakthrough; and frequency of adverse events (AEs), discontinuations, deaths and safety-related laboratory abnormalities.

Efficacy analyses in this study were by serum HBV DNA level, HBV serology, ALT levels, liver function tests and haematology, measured at baseline, weeks 4, 12, 24, 36 and 48, and then every 12 weeks up to week 96. All patients were tested for YMDD mutations at baseline and at weeks 24, 48, 72 and 96 in patients with serum HBV DNA≥60 IU/ml. Genotypic resistance to 3TC and ETV was analysed using the restriction fragment mass polymorphism (RFMP) method, described in detail elsewhere [27–30]. The RFMP results were validated by 100% concordance with those obtained by repetitive direct sequencing. HBsAg and antibody against HBsAg were tested at weeks 48 and 96, while HBeAg and antibody against HBeAg were tested every 6 months. AEs and safety-related clinical laboratory tests were collected at every visit. The proportion of patients with AEs leading to discontinuation in each treatment arm was measured up to week 96. Patients were discontinued from the study if they experienced clinical breakthrough (ALT≥2×ULN on treatment after achieving normalization and serum HBV DNA≥1 log_{10} above nadir) or developed resistance to either of the study drugs. Cirrhosis in this study was defined as either a platelet count <100,000 cells/l with ultrasonographic findings suggestive of cirrhosis including a blunted, nodular liver edge accompanied by splenomegaly (>12 cm), oesophageal or gastric varices, or overt complications of liver cirrhosis including ascites, variceal bleeding and hepatic encephalopathy [31]. A target sample size of ≥25 patients per treatment arm provided ≥80% power to detect up to a 30% difference between two groups (based on Fisher’s exact test with a significance level of 0.05 and assuming a dropout rate of 30% over 2 years). Patients who discontinued prior to week 96 were considered ‘non-completer equals failure’ for the primary end point. In this study, serum HBV DNA levels were logarithmically transformed, with categorical variables expressed as proportions, while continuous variables were expressed as means. Between-group comparisons were performed using a Student’s t-test, or Mann–Whitney U test for continuous variables, and χ² test for categorical variables, as appropriate. Receiver operating characteristic curve and area under the curve for the prediction of virological response to ETV at 96 weeks was calculated. A P-value of <0.05 was considered significant.

This study was approved by independent ethics committees or institutional review boards at each of the study sites and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each of the patients before enrolment. This study was registered with ClinicalTrials.gov (NCT00625560).

Results

Patients

Patient flow through the study is shown in Figure 1. A total of 72 HBeAg-positive patients previously treated with 3TC 100 mg for ≥6 months and with HBV DNA≥60 IU/ml (by PCR) were enrolled, randomized and included in this analysis. Of these, 36 were randomized to the 3TC-maintained group, and 36 to the ETV-switch group. Baseline characteristics for the two treatment groups are shown in Table 1. The mean age was 43 years in both groups, with a mean baseline HBV DNA level of 4.66 log_{10} IU/ml (range 1.98–7.85) and 4.55 log_{10} IU/ml (range 1.99–7.57) for 3TC-maintained and ETV-switch patients, respectively. The mean duration of prior 3TC treatment was 15.1 months in the 3TC-maintained group, and 16.1 months in the ETV-switch group. Cirrhosis was present in 8 (22.2%) patients in each treatment group.

Virological, biochemical and serological response

The proportion of patients achieving the primary end point (undetectable HBV DNA≤60 copies/ml) was greater in the ETV-switch group at weeks 24, 48, 72 and 96 (Figure 2). The mean reduction in serum HBV DNA level was significantly greater in ETV-switch patients than 3TC-maintained patients at weeks 4, 12, 24, 48 and 96 (Figure 3). This difference between the two groups increased at each time point.

At week 48, a higher proportion of patients achieved normalization of ALT in the ETV-switch group than in the 3TC-maintained group (31/36 [86.1%] versus 17/27 [61.5%], respectively; P=0.041). At week 96, ALT normalization was maintained in the majority of ETV-switch patients (29/34; 85.2%).

The proportion of patients achieving HBeAg loss and seroconversion was higher in the ETV-switch group at weeks 24, 48 and 96 (Table 2). No patient from either group achieved HBsAg loss or seroconversion throughout this 96-week analysis.

Predictors of virological response

Patients with baseline HBV DNA<5 log_{10} IU/ml had a higher probability of achieving undetectable HBV DNA (<60 IU/ml) at week 96, than those with baseline HBV DNA≥60 IU/ml. A Student’s t-test was used to determine the statistical significance of differences between two groups. A P-value of <0.05 was considered significant. The mean age was 43 years in both groups, with a mean baseline HBV DNA level of 4.66 log_{10} IU/ml (range 1.98–7.85) and 4.55 log_{10} IU/ml (range 1.99–7.57) for 3TC-maintained and ETV-switch patients, respectively. The mean duration of prior 3TC treatment was 15.1 months in the 3TC-maintained group, and 16.1 months in the ETV-switch group. Cirrhosis was present in 8 (22.2%) patients in each treatment group.

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DNA≥5 log10 IU/ml (100% versus 31.2%; P<0.001). Baseline HBV DNA was the only significant differing factor between those ETV-switch patients achieving a response at week 96, and those who did not (Table 3).

The area under receiver operating characteristic (AUROC) curve for baseline HBV DNA levels to predict virological response to ETV at 96 weeks was 0.905 (95% CI 0.787, 1.000; P<0.001). The diagnostic performance of the HBV DNA 5 log10 IU/ml cutoff to predict virological response to ETV showed 78.3% sensitivity, 100% specificity, 100% positive predictive value, 68.8% negative predictive value, and 85.3% diagnostic accuracy. The AUROC curve for baseline HBV DNA levels to predict 96-week response to ETV are shown in Figure 4.

Virological breakthrough and genotypic resistance
A higher proportion of 3TC-maintained than ETV-switch patients developed genotypic resistance with or without virological breakthrough at all time points. In

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**Figure 1. Patient flow through study**

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3TC-maintained</th>
<th>ETV-switch</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>36</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>23 (63.9)</td>
<td>18 (50)</td>
<td>0.341</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>43 (24–91)</td>
<td>43 (19–68)</td>
<td>0.924</td>
</tr>
<tr>
<td>Prior 3TC treatment duration, months (±se)</td>
<td>15.1 (10.0)</td>
<td>16.1 (10.1)</td>
<td>0.681</td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>8 (22.2)</td>
<td>8 (22.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>HBeAg-positive, n (%)</td>
<td>36 (100)</td>
<td>36 (100)</td>
<td></td>
</tr>
<tr>
<td>Mean HBV DNA, log10 IU/ml (±se)</td>
<td>4.66 (1.69)</td>
<td>4.55 (1.82)</td>
<td>0.788</td>
</tr>
<tr>
<td>Mean ALT, IU/l (±se)</td>
<td>32.6 (16.1)</td>
<td>37.1 (35.5)</td>
<td>0.492</td>
</tr>
<tr>
<td>Mean albumin, g/dl (±se)</td>
<td>4.5 (0.4)</td>
<td>4.5 (0.4)</td>
<td>0.910</td>
</tr>
<tr>
<td>Mean bilirubin, mg/dl (±se)</td>
<td>0.8 (0.4)</td>
<td>0.9 (0.4)</td>
<td>0.390</td>
</tr>
<tr>
<td>Genotypic resistance, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; ETV, entecavir; HBeAg, hepatitis B e antigen; 3TC, lamivudine.
the 29 patients with 3TC-resistant mutations at week 96, the substitutions detected were rtM204I alone \((n=8)\), rtL180M alone \((n=1)\), rtM204I+rtM204V \((n=3)\), rtM204I+rtL180M \((n=4)\), rtM204V+rtL280M \((n=8)\) and rtM204I+rtM204V+rtL180M \((n=5)\). Two ETV-switch patients developed substitutions rtM204V+rtL180M and rtM204I/V+rtL180M at weeks 48 and 72, respectively. One further patient from the ETV-switch group \((1/34; 3.0\%)\) developed resistance-conferring substitutions rtM204V+rtL280M at week 72 with rtS202G and virological breakthrough at week 96. All three patients with substitutions had a baseline HBV DNA level \(\geq 5.0\) log\(_{10}\) IU/ml at the time of switching from 3TC to ETV.

Safety analysis
Both ETV and 3TC were generally well-tolerated. No serious AEs were attributed to either intervention throughout this study. Two 3TC-maintained patients developed HCC and discontinued therapy, one at week 36 in combination with genotypic resistance, virological and biochemical breakthrough, and one at week 84 after developing genotypic resistance and virological breakthrough at week 48. One patient from the ETV-switch group was withdrawn from the study at week 72 following the development of renal cell carcinoma.

Figure 2. Proportion of 3TC-maintained and ETV-switch patients with undetectable HBV DNA<60 IU/ml by PCR

Figure 3. Reduction in mean serum HBV DNA level from baseline in 3TC-maintained and ETV-switch patients through to week 96

ETV, entecavir; HBeAg, hepatitis B e antigen; 3TC, lamivudine.

ETV, entecavir; 3TC, lamivudine.
**Discussion**

In this prospective 96-week study, ETV-switch therapy resulted in superior virological response to 3TC-maintained therapy, with lower rates of genotypic resistance. A greater proportion of patients receiving ETV than 3TC achieved undetectable HBV DNA and ALT normalization at all time points. High rates of genotypic resistance with virological breakthrough were observed in 3TC-maintained patients, with considerably lower levels seen in patients who were switched to ETV. Genotypic resistance with virological breakthrough in this study was seen in 82.9% of 3TC-maintained patients and 2.9% of ETV-switch patients by week 96. However, two ETV-switch patients developed substitutions rtM204V+rtL180M and rtM204I/V+rtL180M at weeks 48 and 72, respectively. These patients did not have M204V/I mutations in the YMDD motif at baseline. A long-term follow-up study is required to determine the long-term efficacy and resistance development of the ETV-switch therapy in CHB patients with suboptimal virological response to 3TC. This study also found that baseline HBV DNA <5.0 \( \log_{10} \) IU/ml was a predictor for virological response to ETV at 96 weeks, supporting previously reported data in 3TC-refractory patients [32]. The safety profile of ETV in this cohort of patients with a PVR to 3TC was favourable and consistent with both the general HBV population and data from previously reported 3TC-pretreated patients. Although there was a previous report [33] on the effect of ETV in 3TC-experienced patients without 3TC.

**Table 2.** Serological responses through week 96 in 3TC-maintained and ETV-switch patients who previously had a partial virological response to 3TC monotherapy

<table>
<thead>
<tr>
<th>Time point</th>
<th>3TC-maintained</th>
<th>ETV-switch</th>
<th>3TC-maintained</th>
<th>ETV-switch</th>
<th>3TC-maintained</th>
<th>ETV-switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 24</td>
<td>2.8 (1/36)</td>
<td>8.3 (3/36)</td>
<td>2.8 (1/36)</td>
<td>5.6 (2/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
</tr>
<tr>
<td>Week 48</td>
<td>5.7 (2/35)</td>
<td>11.1 (4/36)</td>
<td>2.9 (1/35)</td>
<td>8.3 (3/36)</td>
<td>0 (0/35)</td>
<td>0 (0/36)</td>
</tr>
<tr>
<td>Week 72</td>
<td>2.9 (1/35)</td>
<td>13.9 (5/36)</td>
<td>2.9 (1/35)</td>
<td>8.3 (3/36)</td>
<td>0 (0/35)</td>
<td>0 (0/36)</td>
</tr>
<tr>
<td>Week 96</td>
<td>5.7 (2/35)</td>
<td>17.6 (6/34)</td>
<td>2.9 (1/35)</td>
<td>8.8 (3/34)</td>
<td>0 (0/35)</td>
<td>0 (0/34)</td>
</tr>
</tbody>
</table>

Data are percentage \( n/\text{total} \). Missing values handled with ‘non-completer equals failure’ method. Two entecavir (ETV)-switch and one lamivudine (3TC)-maintained patient withdrew consent and were not included in this analysis. HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

**Table 3.** Comparison of baseline characteristics in ETV-switch patients with and without a virological response at week 96

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Virological response</th>
<th>No virological response</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>23</td>
<td>11</td>
<td>–</td>
</tr>
<tr>
<td>Male, n (%</td>
<td>10 (43.4)</td>
<td>6 (54.5)</td>
<td>0.717</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>42 (19–65)</td>
<td>47 (29–68)</td>
<td>0.371</td>
</tr>
<tr>
<td>Prior 3TC treatment duration, months (( \pm )se)</td>
<td>16.0 (10.1)</td>
<td>16.4 (11.2)</td>
<td>0.925</td>
</tr>
<tr>
<td>Cirrhosis, n (%</td>
<td>7 (30.4)</td>
<td>1 (9.1)</td>
<td>0.227</td>
</tr>
<tr>
<td>Mean HBV DNA, ( \log_{10} ) IU/ml (( \pm )se)</td>
<td>3.73 (1.47)</td>
<td>6.35 (0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ALT, IU/l (( \pm )se)</td>
<td>38.10 (33.20)</td>
<td>25.30 (11.00)</td>
<td>0.105</td>
</tr>
<tr>
<td>Mean albumin, g/dl (( \pm )se)</td>
<td>4.50 (0.50)</td>
<td>4.50 (0.30)</td>
<td>0.179</td>
</tr>
<tr>
<td>Mean bilirubin, mg/dl (( \pm )se)</td>
<td>0.80 (0.30)</td>
<td>1.00 (0.50)</td>
<td>0.179</td>
</tr>
</tbody>
</table>

Two entecavir (ETV)-switch and one lamivudine (3TC)-maintained patients withdrew consent and were not included in this analysis. ALT alanine transaminase; HBeAg hepatitis B e antigen.
resistance, this is the first study to prospectively compare ETV-switch versus 3TC-maintained therapy in Asian patients with a PVR to prior 3TC therapy.

The patient population studied here is representative of a large number of CHB patients from Korea for whom 3TC therapy has been used as a first-line therapy. These patients represent a therapeutic challenge in that they did not respond well to 3TC therapy following ≥6 months of therapy, despite the absence of baseline YMDD mutations associated with resistance and treatment failure. These patients are not well-addressed in currently available clinical practice guidelines, with the exception of the European Association for the Study of the Liver’s 2009 update on the management of CHB. This guideline recommends switching to a more potent drug, such as ETV or TDF, preferentially without cross-resistance [24]. TDF is not currently available in most Asia-Pacific countries, including Korea, and cost of therapy may be a barrier to using this drug across this region. The results presented here may support the use of ETV in patients with a PVR although close resistance monitoring should be considered. While combination therapy may offer an advantage over sequential monotherapy, the benefits have not yet been conclusively demonstrated. The cost and long-term safety of combination or add-on therapy also remain unknown, with cases of renal impairment reported with adefovir and 3TC combination therapy in 3TC-refractory patients [34]. Additionally, this study found that lower viral load at the time of switch was a predictor for response to ETV therapy, but whether this can be utilized in a clinical setting to identify patients suitable for therapy would require further study. Greater proportions of ETV-switch than 3TC-maintained patients achieved HBeAg loss and seroconversion, a marker for treatment success in some clinical practice guidelines [11]. Further supporting evidence is required to determine whether this represents an opportunity to stop therapy in this patient group.

There are several features of the study design that should be considered when interpreting the findings presented here. The protocol did not include measuring HBV genotype, which is known to influence response to treatment [3,5]. HBV infection in Korea is almost exclusively genotype C (>95%), whereas HBV genotypes B and C coexist in the majority of the Asia-Pacific region [6,35–37]. Therefore, the results of this study may be applied with discretion to other Asian patient cohorts. Further studies of 3TC-pretreated patients switched to ETV and stratified by HBV genotype may be beneficial in order to generalize this finding. Most important to note is the 1.0 mg ETV dose used in this study. The safety of ETV 1.0 mg is similar to that of the 0.5 mg dose; however, it is currently not licensed for suboptimal 3TC responders in Korea. Data are limited on the use of the 0.5 mg ETV dose in 3TC-pretreated patients. Previously reported Japanese data suggest that the 0.5 and 1.0 mg ETV doses are equally efficacious in 3TC-refractory patients at week 48, however, there was no long-term follow up in this study [38]. The study presented here represents the first prospective, well-designed clinical trial investigating the use of 96 weeks 1.0 mg ETV in patients with a PVR to 3TC. Further long-term follow-up studies of Asian 3TC-pretreated patients using ETV are therefore warranted.

In this study, switching to ETV in patients with a PVR to 3TC resulted in increased virological efficacy and lower rates of antiviral resistance than maintaining 3TC. Switching treatment after the development of drug resistance may not provide an optimal response, therefore a timely switch to a drug with potent viral suppression and low genotypic resistance, such as ETV, may be recommended in patients with a PVR to 3TC.

Acknowledgements

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Disclosure statement

K-HH and SHA have acted as advisors and lecturers for Bayer, Bristol–Myers Squibb, Gilead Sciences, GlaxoSmitKline, Hoffmann-La Roche, Merck and Novartis/Idenix Pharmaceuticals. All other authors declare no competing interests.

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