Efficacy of Entecavir With or Without Tenofovir Disoproxil Fumarate for Nucleos(t)ide-Naïve Patients With Chronic Hepatitis B

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See Pan CQ et al on page 1047 in *CGH*.

BACKGROUND & AIMS: Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are potent antiviral agents that might have additive or synergistic antiviral activity in treatment of patients with chronic hepatitis B (CHB). We compared the efficacy and safety of ETV monotherapy with those of a combination of ETV and TDF. **METHODS:** We performed a randomized, open-label, multicenter, superiority study of 379 nucleos(t)ide-naïve patients with hepatitis B e antigen (HBeAg)-positive (n = 264) or HBeAg-negative (n = 115) CHB. Subjects were given ETV 0.5 mg (n = 182) or a combination of ETV 0.5 mg and TDF 300 mg (n = 197) for 100 weeks. **RESULTS:** At week 96, comparable proportions of patients in each study arm achieved the primary end point of a level of hepatitis B virus (HBV) DNA <50 IU/mL (83.2% vs 76.4%; $P = .088$). Among HBeAg-positive patients, a greater proportion given combination therapy achieved levels of HBV DNA <50 IU/mL than those given ETV alone (80.4% vs 69.8%; $P = .046$). However, this difference was observed only in patients with baseline levels of HBV DNA $\geq 10^8$ IU/mL (79% vs 62%) and not in those with baseline levels of HBV DNA $<10^8$ IU/mL (83% in both arms). Rates of HBeAg loss and HBeAg seroconversion were comparable between groups, whereas the rate of alanine aminotransferase normalization was greater in the ETV monotherapy group. No HBV variants associated with ETV or TDF resistance were detected. Safety profiles were consistent with previous reports of ETV or TDF monotherapy. **CONCLUSIONS: The antiviral efficacy of ETV monotherapy is comparable to that of ETV plus TDF in a mixed population of nucleos(t)ide-naïve patients with CHB (70% HBeAg positive). The combination therapy could provide an incremental benefit to HBeAg-positive patients with baseline levels of HBV DNA $\geq 10^8$ IU/mL. Clinical trial information: ETV-110, the BE-LOW study; NCT00410072.**

Keywords: Antiviral Therapy; Nucleos(t)ide Analogue; Hepatitis B e Antigen; ALT.

The aim of chronic hepatitis B (CHB) treatment is the durable suppression of hepatitis B virus (HBV) replication, with the goals of preventing cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[1,2] A long duration of nucleos(t)ide analogue (NA) therapy is usually required to achieve a sustained response. Antiviral therapy that results in rapid and maximal viral suppression and has a high genetic barrier to resistance is most likely to achieve and maintain virologic suppression during long-term use.[3] The combination of 2 or more potent NAs may provide additive or synergistic antiviral activity, which may result in faster or more profound viral suppression. In the treatment of human immunodeficiency virus infection, combination therapy is well established as superior to sequential monotherapy in terms of efficacy and prevention of drug resistance and is the current standard of care.[4] In CHB, few studies exploring the combination of 2 NAs in treatment-naïve patients have been reported to date. With the first-generation NAs adefovir dipivoxil and lamivudine, 2 years of combination therapy with both agents was more effective in terms of HBV DNA suppression and alanine aminotransferase (ALT) normalization and was associated with a lower rate of resistance development than lamivudine monotherapy; however, serologic responses were comparable between the 2 treatment groups.[5] In a study with telbivudine and lamivudine, rates of HBV DNA suppression and ALT normalization after 1 year of treatment were not significantly different between the combination of both agents and telbivudine alone, and the rate of virologic breakthrough was higher with the combination therapy.[6]

Among the approved NAs, entecavir (ETV) and tenofovir disoproxil fumarate (TDF) have potent antiviral activity[7] and are currently recommended as first-line monotherapies for CHB.[1,2] Both drugs achieved high rates of HBV DNA suppression and ALT normalization in phase 3 studies in hepatitis B e antigen (HBeAg)-positive and in HBeAg-negative patients and showed maintenance of viral

Abbreviations used in this paper: CHB, chronic hepatitis B; ETV, entecavir; NA, nucleos(t)ide analogue; NC=F, noncompleters = failures; NC=M, noncompleters = missing; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

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suppression in long-term studies.[8–15] In addition, both ETV and TDF are associated with low rates of resistance development in NA-naïve patients during long-term therapy[16–18] and have a nonoverlapping pattern of resistance substitutions,[1] making these 2 NAs potential candidates for combination therapy. Both drugs showed favorable safety profiles over 5 years.[15,19] However, some adverse events have been reported, including mild renal impairment,[20] in particular with TDF,[21] or lactic acidosis with ETV in patients with decompensated liver disease and high Model for End-Stage Liver Disease scores (≥22),[22] which could potentially be exacerbated with combined treatment.

The objective of this study was to evaluate the efficacy and safety of ETV plus TDF combination therapy compared with ETV monotherapy in NA-naïve patients with HBeAg-positive or HBeAg-negative CHB.

Patients and Methods

Study Design

This was a randomized, open-label, multicenter, phase 3b superiority study (ETV-110, the BE-LOW study; NCT00410072) in NA-naïve HBeAg-positive or HBeAg-negative patients with CHB. Patients were randomized 1:1 to receive ETV 0.5 mg plus TDF 300 mg once daily or ETV 0.5 mg once daily for 100 weeks, with the primary end point measurement at week 96. To test whether patients with high viral load might derive greater benefit from combination therapy, the total number of HBeAg-negative patients was capped at 30%. Randomized treatment assignments were generated by a central randomization center and provided to sites during individual patient enrollment using an interactive voice response system. Patients were randomized using a block design stratified by investigative site and HBeAg status. At the end of study dosing, further treatment with commercially available therapies was at the discretion of the investigator. All subjects who discontinued treatment at or before week 100 entered a follow-up period for up to 24 weeks.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the regulatory requirements of all participating countries. Institutional approval was obtained at all clinical sites, and written informed consent was provided by all study participants.

Patients

Patients were enrolled between April 2007 and November 2008 by the study investigator in 69 centers from 13 countries. Eligible patients were male or female, aged 16 years or older, with HBeAg-positive or HBeAg-negative CHB (detectable hepatitis B surface antigen [HBsAg] at screening and for ≥24 weeks before screening or detectable HBsAg for <24 weeks and negative immunoglobulin M core antibody) and compensated liver function (international normalized ratio ≤1.5, serum albumin level ≥3 g/dL, serum total bilirubin level ≤2.5 mg/dL). At screening, serum HBV DNA values were required to be >172,000 IU/mL (approximately 10^6 copies/mL) in HBeAg-positive patients and >17,200 IU/mL (approximately 10^5 copies/mL) in HBeAg-negative patients. ALT values were required to be ≥1.3 times and ≤10 times the upper limit of normal (ULN; 48 U/L for male patients and 37 U/L for female patients) based on results of the central testing laboratory, at screening, and at least once ≥12 weeks before screening.

Efficacy Analyses

The primary efficacy end point was the proportion of patients achieving an HBV DNA level <50 IU/mL (approximately 300 copies/mL) at week 96. Selected secondary efficacy end points included the proportion of patients achieving an HBV DNA level <50 IU/mL at week 48 and the proportion of patients at weeks 48 and 96 achieving an HBV DNA level <50 IU/mL by HBeAg status, ALT normalization (≤1 times ULN), HBeAg loss and HBeAg seroconversion (among those HBeAg positive), and HBsAg loss. The mean values of HBV DNA were calculated at baseline, week 4, and from week 12 onward at 12-week intervals through week 96. The incidence of virologic breakthrough (confirmed ≥1-$\log_{10}$ increase in HBV DNA level from nadir) and cumulative probability of HBV antiviral drug resistance were determined through week 96. Sequencing of HBV polymerase was performed on all baseline samples and on-treatment samples from patients with an HBV DNA level >50 IU/mL at weeks 48 or 96 or last study visit if treatment was discontinued prematurely and at the time of virologic breakthrough.

Safety Analyses

Cumulative safety was assessed through week 96. HBV-related outcomes, including ALT flares, hepatic decompensation, and HCC, were also assessed during a 24-week off-treatment follow-up period. The frequencies of serious adverse events and deaths were reported for all enrolled patients, and other safety evaluations were based on treated patients. ALT flares were defined as ALT levels >2 times baseline and >10 times ULN. Plasma phosphate levels were not monitored, and plasma lactate levels were measured only in patients with suspected lactic acidosis.

Assay Methodology

Data were collected at the investigator's site and central laboratory. Serum HBV DNA level was measured using the Roche Cobas TaqMan HPS assay (Branchburg, NJ) (lower limit of detection, 10 IU/mL [approximately 58 copies/mL]). Antiviral drug resistance mutation was determined using the Trugene HBV genotyping assay (Bayer, Tarrytown, NY), which is based on population sequencing of the HBV polymerase gene. Cumulative probabilities of genotypic resistance and virologic breakthrough with resistance were calculated as described previously.[23] Cumulative probabilities were calculated separately for resistance to ETV (amino acid substitutions at M204 ± L180 + T184 or S202 or M250) and to TDF (amino acid substitutions at A181, N236, or A194 + M204).

Statistical Analysis

Efficacy analyses were based on patients who received at least one dose of study medication (modified intent-to-treat analysis). Patients who discontinued study medication before week 96 were considered treatment failures (NC=F). An analysis in which noncompleting patients were not evaluated (NC=M) was also performed. A sample size of 384 randomized patients (approximately 192 per arm) was estimated to provide >80% power to show superiority of ETV plus TDF versus ETV alone for the primary end point at week 96 for the overall patient population, assuming a response rate (NC=F) of 85% for combination therapy and 70% for monotherapy among HBeAg-

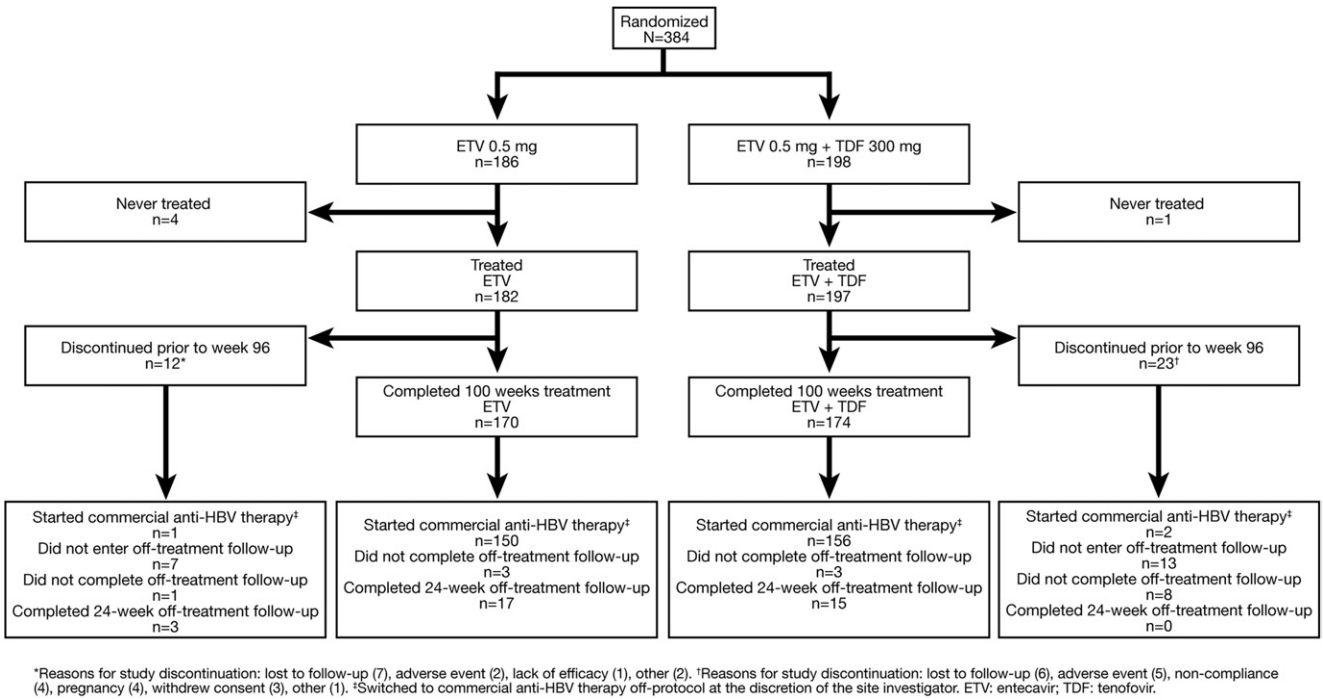

Figure 1. Disposition of study patients.

positive patients and 95% for combination therapy and 90% for monotherapy among HBeAg-negative patients and that 70% of the patients would be HBeAg positive and 30% HBeAg negative. In the absence of any clinical data on the ETV plus TDF combination, the projected response rates for the combination arm were selected based on clinical assessment of what increment in response might warrant the additional risks and expense of dual nucleos(t)ide exposure. The sample size also provided 80% power to show superiority for the secondary end point of the proportion of patients with an HBV DNA level <50 IU/mL at week 96 for ETV plus TDF compared with ETV monotherapy for the subset of HBeAg-positive patients.

Categorical variables were summarized by counts and percentages. Comparisons of binary variables were based on Cochran–Mantel–Haenszel statistics stratified by HBeAg status. For the primary end point and the prespecified secondary end point (proportion of patients with an HBV DNA level <50 IU/mL at week 96, overall, and for HBeAg-positive patients), ETV plus TDF was considered superior to ETV alone if the *P* value was <.05. Continuous variables were summarized with descriptive statistics and compared using the 2-sided *t* test based on linear regression adjusting for baseline measurements. Unplanned post hoc statistical comparisons were performed for other secondary end points of interest, including week 96 HBeAg loss, HBeAg seroconversion, and ALT normalization. The *P* values presented for these secondary end points were not adjusted for multiple comparisons. A post hoc exploratory analysis assessed the proportion of HBeAg-positive patients by baseline HBV DNA level (subgroups $<10^8$ IU/mL vs $\geq 10^8$ IU/mL) in each treatment group who achieved an HBV DNA level <50 IU/mL at weeks 48 and 96. Additional analyses evaluated rates of HBeAg loss and seroconversion by baseline ALT level and HBV genotype and rates of ALT normalization by baseline body mass index.

Results

Patient Population

Of the 384 patients randomized in this study, 379 were treated with ETV plus TDF (n = 197) or ETV alone (n = 182) (Figure 1 and Supplementary Figure 1). More patients in the combination arm than in the monotherapy arm discontinued therapy before week 96 (23 [11.6%] vs 12 [6.5%]), but this difference was not statistically significant (*P* = .11). The most common reasons for treatment discontinuation were lost to follow-up (ETV + TDF, 6; ETV, 7) and adverse events (ETV + TDF, 5; ETV, 2). At the end of study treatment (early discontinuation or at week 100), 309 patients received commercial anti-HBV therapies, whereas 50 patients entered off-treatment follow-up. The baseline demographics and disease characteristics were generally well balanced across treatment groups (Table 1), with approximately 50% Asian and 50% white patients and 70% HBeAg-positive and 30% HBeAg-negative patients in both arms. The mean baseline HBV DNA level was 7.5 $\log_{10}$ IU/mL overall in both arms and approximately 2 $\log_{10}$ IU/mL higher among HBeAg-positive patients than among HBeAg-negative patients (Table 1). In the combination therapy arm, baseline ALT levels were higher, with a mean of 158 U/L compared with 127 U/L in the monotherapy arm, and there were more male patients (ETV + TDF, 74.1%, ETV, 63.7%).

Virologic Response

At week 96, no significant difference for the primary efficacy end point was observed between the 2 treatment arms (Figure 2*A*). Among patients receiving ETV

Table 1. Baseline Demographics and Disease Characteristics

	ETV 0.5 mg (n = 182)	ETV 0.5 mg + TDF 300 mg (n = 197)
Age (*y*), mean (SE)	40 (1.1)	39 (1.0)
Male, n (%)	116 (63.7)	146 (74.1)
Race, n (%)		
Asian	84 (46.2)	102 (51.8)
White	83 (45.6)	87 (44.2)
Black	10 (5.5)	4 (2.0)
Native Hawaiian/Pacific Islander	1 (0.5)	1 (0.5)
Other	4 (2.2)	3 (1.5)
HBeAg status, n (%)		
HBeAg positive	126 (69.2)	138 (70.1)
HBeAg negative	56 (30.8)	59 (29.9)
HBV DNA, *mean log_{10} IU/mL* (SE)		
Overall	7.5 (0.11)	7.5 (0.10)
HBeAg positive	8.10 (0.09)	8.15 (0.08)
HBeAg negative	6.09 (0.18)	6.09 (0.15)
HBV genotype, n/N (%)		
A		
Overall	38/182 (20.9)	36/197 (18.3)
HBeAg positive	30/126 (23.8)	33/138 (23.9)
HBeAg negative	8/56 (14.3)	3/59 (5.1)
B		
Overall	38/182 (20.9)	35/197 (17.8)
HBeAg positive	24/126 (19.0)	22/138 (15.9)
HBeAg negative	14/56 (25.0)	13/59 (22.0)
C		
Overall	35/182 (19.2)	53/197 (26.9)
HBeAg positive	30/126 (23.8)	44/138 (31.9)
HBeAg negative	5/56 (8.9)	9/59 (15.3)
D		
Overall	55/182 (30.2)	57/197 (28.9)
HBeAg positive	30/126 (23.8)	28/138 (20.3)
HBeAg negative	25/56 (44.6)	29/59 (49.2)
Other[a]		
Overall	12/182 (6.6)	16/197 (8.1)
HBeAg positive	8/126 (6.3)	11/138 (8.0)
HBeAg negative	4/56 (7.1)	5/59 (8.5)
Missing		
Overall	4/182 (2.2)	0/197
HBeAg positive	4/126 (3.2)	0/138
HBeAg negative	0/56	0/59
ALT		
Mean *U/L* (SE)	127 (7.3)	158 (13.1)
Categories, n/N (%)		
<2 times ULN		
Overall	76/182 (41.8)	79/197 (40.1)
HBeAg positive	47/126 (37.3)	52/138 (37.7)
HBeAg negative	29/56 (51.8)	27/59 (45.8)
2–5 times ULN		
Overall	86/182 (47.3)	86/197 (43.7)
HBeAg positive	64/126 (50.8)	61/138 (44.2)
HBeAg negative	22/56 (39.3)	25/59 (42.4)
>5 times ULN		
Overall	20/182 (11.0)	32/197 (16.2)
HBeAg positive	15/126 (11.9)	25/138 (18.1)
HBeAg negative	5/56 (8.9)	7/59 (11.9)

[a]HBV genotype E, F, mixed, or indeterminate.

plus TDF, 83.2% (164/197) had an HBV DNA level <50 IU/mL at week 96 compared with 76.4% (139/182) receiving ETV alone ($P = .088$). At week 48, 80.2% of patients in the ETV plus TDF arm achieved an HBV DNA level <50 IU/mL compared with 70.3% in the ETV monotherapy arm ($P = .026$). Likewise, the mean change from baseline in serum HBV DNA level was slightly greater during the first 48 weeks in the combination arm and was comparable between treatment arms at week 96 ($P = .25$; Table 2 and Figure 3*A*).

Analysis of the virologic response according to baseline HBeAg status showed that among HBeAg-positive patients, a higher proportion of patients in the combination therapy arm than in the monotherapy arm had an HBV DNA level <50 IU/mL at week 48 (80.2% vs 70.3%; $P = .018$) and at week 96 (80.4% vs 69.8%; $P = .046$; Figure 2*B*). In contrast, among HBeAg-negative patients, comparable proportions of patients in both arms achieved HBV DNA levels <50 IU/mL at week 48 (93.2% vs 91.1%; $P = .67$) and at week 96 (89.8% vs 91.1%; $P = .82$; Figure 2*C*). Similar results were obtained when noncompleting patients were excluded from the analysis (NC=M; Supplementary Table 1). The mean change from baseline in serum HBV DNA level at week 96 was slightly greater with the combination treatment in HBeAg-positive patients ($P = .04$) and comparable in HBeAg-negative patients (Table 2 and Figure 3*B*). To determine the impact of baseline viral load on the response to treatment, a post hoc exploratory analysis was performed. Among HBeAg-positive patients with a baseline HBV DNA level $\geq 10^8$ IU/mL, 79% of patients in the combination arm achieved an HBV DNA level <50 IU/mL at week 96 compared with 62% in the ETV monotherapy arm ($P = .018$), whereas comparable results in the 2 treatment arms were observed in patients with a baseline HBV DNA level $<10^8$ IU/mL (83% in both groups; Figure 2*D*).

Biochemical and Serologic Response

Through week 96, 81.9% of patients treated with ETV alone achieved normalization of ALT levels compared with 69.0% in the combination therapy arm ($P = .004$). Among HBeAg-positive patients, comparable proportions of patients in the monotherapy arm and combination therapy arm achieved HBeAg loss (38.9% vs 29.7%; $P = .16$) and HBeAg seroconversion (32.5% vs 21.7%; $P = .08$) (Table 2). The rates of HBsAg loss (2.7% vs 3.6%) and HBsAg seroconversion (1.1% vs 2.0%) were low in both treatment groups (Table 2). Similar results were obtained when patients who discontinued study medication before week 96 were counted as missing (Supplementary Table 1). All patients who achieved HBsAg loss at week 48 or 96 also had an HBV DNA level <50 IU/mL at that visit. Among patients with HBeAg seroconversion at week 48 or 96, all had an HBV DNA level <50 IU/mL at that visit, except 2 patients (1 in each arm) who had HBeAg seroconversion at week 48 without complete virologic response; both of these patients maintained HBeAg seroconversion and had an HBV DNA level <50 IU/mL at week 96. Rates of HBeAg loss and HBeAg seroconversion by baseline ALT level and HBV genotype were assessed post hoc (Table 2). Among HBeAg-positive patients with a baseline ALT level <2.0 times ULN or

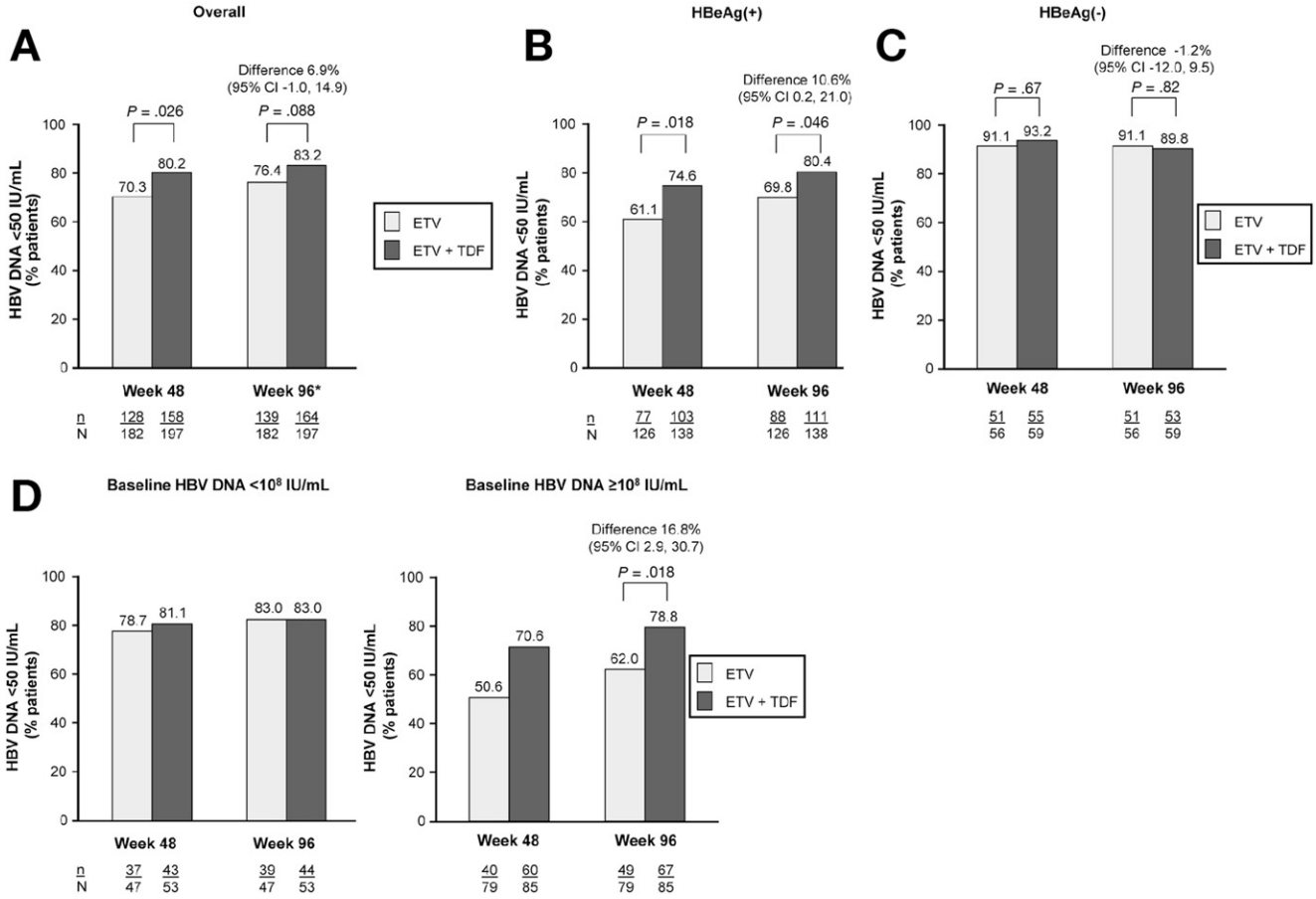

Figure 2. Virologic response (HBV DNA level <50 IU/mL) at weeks 48 and 96 in (*A*) all patients, (*B*) HBeAg-positive patients, (*C*) HBeAg-negative patients, and (*D*) HBeAg-positive patients with baseline HBV DNA level $<10^8$ IU/mL or $\geq 10^8$ IU/mL. *Primary end point.

2–5 times ULN, the proportion of patients with HBeAg loss and HBeAg seroconversion at week 96 was higher for the ETV arm than for the ETV plus TDF arm but was similar for patients with a baseline ALT level >5 times ULN (Table 2). Analysis of the serologic response in HBeAg-positive patients according to HBV genotype did not reveal any correlation.

Resistance and Virologic Breakthrough

Over the 96-week treatment period, 7 (3.6%; 5 HBeAg positive, 2 HBeAg negative) patients treated with ETV plus TDF and 2 (1.0%; 1 HBeAg positive, 1 HBeAg negative) patients treated with ETV alone experienced virologic breakthrough. Population sequencing showed that none of the patients with virologic breakthrough, or with an HBV DNA level >50 IU/mL at week 48 or 96, had HBV with amino acid substitutions that have been reported to be associated with ETV resistance or reduced TDF susceptibility.[1]

Safety

The mean time on therapy was 97 weeks in the combination therapy arm and 94 weeks in the monotherapy arm. Five patients in the combination therapy arm and 2 patients in the monotherapy arm discontinued study therapy due to adverse events. The cumulative safety profiles were similar between both treatment groups, with comparable frequencies of adverse events and serious adverse events (Table 3). Elevations of creatinine level by ≥0.3 mg/dL were observed with similar frequencies across both arms (ETV, 6 [3.3%]; ETV + TDF, 4 [2.0%]). Elevations of creatinine level by ≥0.5 mg/dL were more frequent in patients receiving ETV monotherapy (ETV, 3 [1.6%]; ETV + TDF, 0); none of the patients required dose reduction, and the increase in creatinine level resolved with continued therapy in all 3 patients.

On-treatment ALT flares were reported in 3 HBeAg-positive patients (ETV, 1; ETV + TDF, 2); all occurred at approximately 24 weeks of treatment and were associated with a reduction in HBV DNA level and subsequent HBeAg seroconversion. Of the 50 patients who entered off-treatment follow-up, 35 patients completed 24 weeks of follow-up; of these, 7 were HBeAg negative and 28 were HBeAg positive at baseline. Among those HBeAg positive at baseline, 13 remained HBeAg positive and 15 lost HBeAg, of whom 13 underwent HBeAg seroconversion, before stopping treatment. None of the 15 patients with HBeAg loss experienced serologic relapse during follow-up. None of the 35 patients completing the off-treatment follow-up experienced off-treatment flares; 8 had an HBV DNA level <50 IU/mL and

Table 2. Virologic, Biochemical, and Serologic Responses at Weeks 48 and 96

	ETV (n = 182)		ETV + TDF (n = 197)	
	Week 48	Week 96	Week 48	Week 96
HBV DNA mean change from baseline, *log_{10} IU/mL* (SE)				
Overall	−5.57 (0.10)	−5.77 (0.11)	−5.99 (0.10)	−5.96 (0.12)
HBeAg positive	−6.05 (0.10)	−6.30 (0.10)	−6.57 (0.08)	−6.62 (0.10)
HBeAg negative	−4.54 (0.16)	−4.61 (0.17)	−4.66 (0.16)	−4.58 (0.17)
ALT normalization				
Overall	151/182 (83.0)	149/182 (81.9)	143/197 (72.6)	136/197 (69.0)
HBeAg positive	102/126 (81.0)	103/126 (81.7)	97/138 (70.3)	89/138 (64.5)
HBeAg negative	49/56 (87.5)	46/56 (82.1)	46/59 (78.0)	47/59 (79.7)
HBeAg loss[a]				
Overall, n/N (%)	32/126 (25.4)	49/126 (38.9)	27/138 (19.6)	41/138 (29.7)
By HBV genotype, n/N[b] (%)				
A	11/30 (36.7)	16/30 (53.3)	5/33 (15.2)	11/33 (33.3)
B	8/24 (33.3)	9/24 (37.5)	5/22 (22.7)	6/22 (27.3)
C	4/30 (13.3)	3/30 (10.0)	9/44 (20.5)	14/44 (31.8)
D	6/30 (20.0)	13/30 (43.3)	3/28 (10.7)	6/28 (21.4)
Other[c]	3/8 (37.5)	7/8 (87.5)	5/11 (45.5)	4/11 (36.4)
By baseline ALT, n/N[d] (%)				
<2 times ULN	6/47 (12.8)	14/47 (29.8)	5/52 (9.6)	11/52 (21.2)
2–5 times ULN	21/64 (32.8)	29/64 (45.3)	11/61 (18.0)	18/61 (29.5)
>5 times ULN	5/15 (33.3)	6/15 (40.0)	11/25 (44.0)	12/25 (48.0)
HBeAg seroconversion[a]				
Overall, n/N (%)	28/126 (22.2)	41/126 (32.5)	25/138 (18.1)	30/138 (21.7)
By HBV genotype, n/N[b] (%)				
A	7/30 (23.3)	11/30 (36.7)	5/33 (15.2)	7/33 (21.2)
B	8/24 (33.3)	9/24 (37.5)	5/22 (22.7)	6/22 (27.3)
C	4/30 (13.3)	3/30 (10.0)	8/44 (18.2)	9/44 (20.5)
D	6/30 (20.0)	11/30 (36.7)	2/28 (7.1)	4/28 (14.3)
Other[c]	3/8 (37.5)	6/8 (75)	5/11 (45.5)	4/11 (36.4)
By baseline ALT, n/N[d] (%)				
<2 times ULN	6/47 (12.8)	12/47 (25.5)	4/52 (7.7)	6/52 (11.5)
2–5 times ULN	18/64 (28.1)	24/64 (37.5)	11/61 (18.0)	15/61 (24.6)
>5 times ULN	4/15 (26.7)	5/15 (33.3)	10/25 (40.0)	9/25 (36.0)
HBsAg loss, n/N (%)				
Overall	4/182 (2.2)	5/182 (2.7)	2/197 (1.0)	7/197(3.6)
HBeAg positive	4/126 (3.2)	5/126 (4.0)	2/138 (1.4)	7/138 (5.1)
HBeAg negative	0/56	0/56	0/59	0/59
HBsAg seroconversion, n/N (%)				
Overall	1/182 (0.5)	2/182 (1.1)	1/197 (0.5)	4/197 (2.0)
HBeAg positive	1/126 (0.8)	2/126 (1.6)	1/138 (0.7)	4/138 (2.9)
HBeAg negative	0/56	0/56	0/59	0/59

NOTE. Patients who discontinued study medication before week 96 were considered treatment failures (NC=F; intention-to-treat population).
[a]Among those HBeAg positive at baseline.
[b]N = total number of patients per HBV genotype; patients with missing HBV genotype result were not included.
[c]HBV genotype E, F, mixed, or indeterminate.
[d]N = total number of patients per baseline ALT category.

7 had an HBV DNA level <1000 IU/mL at last off-treatment follow-up. Among the 15 patients who did not complete the off-treatment follow-up, none experienced off-treatment flares through the last visit.

During treatment and postdosing follow-up, malignancies were diagnosed in 4 patients treated with ETV (3 HCC; 1 gastric cancer) and in 1 patient treated with ETV plus TDF (breast cancer). All 3 patients with HCC had an HBV DNA level <50 IU/mL at the time of diagnosis and were diagnosed between 261 and 736 days after treatment initiation (2 on-treatment, 1 off-treatment); 2 of these patients had cirrhosis before study treatment. Three deaths were reported on treatment or during off-treatment follow-up, all of which occurred in the combination therapy arm. The investigator-assigned causes of death were bile duct tumor (1), cardiac arrest likely due to an acute myocardial infarction (1), and liver failure (1). The patient who died from liver failure was a 70-year-old, HBeAg-positive, Asian woman randomized to the ETV plus TDF arm. She had a >5-log_{10} decrease in HBV DNA level by week 24 to a nadir of 1.8 log_{10} IU/mL and experienced breakthrough at week 48. The patient remained on ETV plus TDF treatment, with a normal ALT level and an HBV DNA level 7.48 log_{10} IU/mL at week 100. At week 100, the patient continued treatment with commercial ETV and TDF. Five days later, the patient was hospitalized for fatigue and jaundice and died 1 week after admission. Sequencing of stored samples from base-

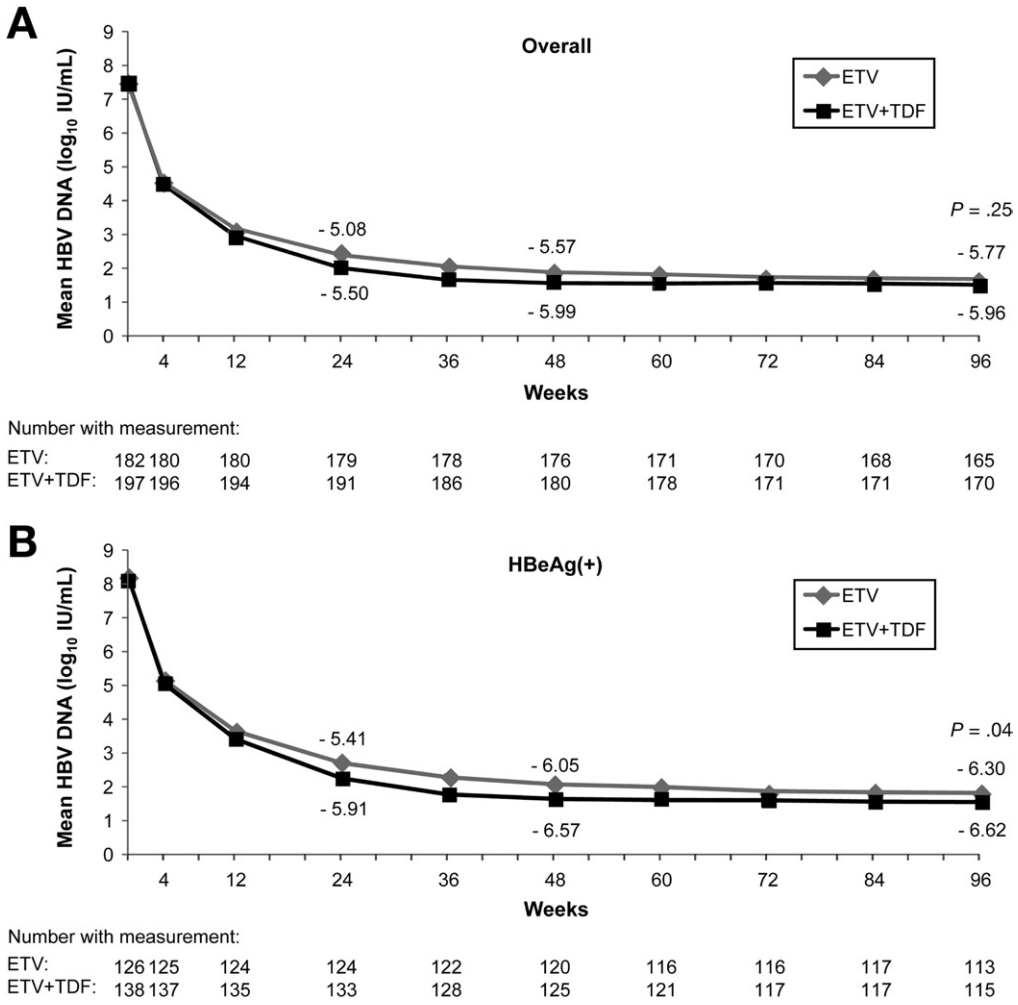

Figure 3. Mean HBV DNA levels through week 96, (*A*) overall and (*B*) in HBeAg-positive patients. Indicated are the mean changes from baseline at weeks 24, 48, and 96 for each treatment and the *P* values for the difference in mean change from baseline at week 96 between treatments.

line, week 48, and week 96 did not show any amino acid substitutions associated with ETV or TDF resistance.

Discussion

In this study, which included a mixed population of NA-naïve HBeAg-positive and HBeAg-negative patients with compensated CHB, the antiviral efficacy of ETV monotherapy was comparable to that of ETV plus TDF. At week 96, combined treatment with ETV plus TDF did not result in a higher proportion of patients with an HBV DNA level <50 IU/mL, ALT normalization, HBeAg loss, or HBeAg seroconversion compared with ETV monotherapy. When the responses of HBeAg-positive and HBeAg-negative patients were analyzed separately, treatment with ETV plus TDF in HBeAg-positive patients resulted in a higher proportion ($P = .046$) achieving an HBV DNA level <50 IU/mL and a greater reduction from baseline in mean serum HBV DNA level at week 96. However, the superiority of combination therapy was observed only in HBeAg-positive patients with a baseline HBV DNA level $\geq 10^8$ IU/mL, not in those with a baseline HBV DNA level $<10^8$ IU/mL. Previous studies have shown that even with potent agents such as ETV and TDF, it takes longer for patients starting from high levels of viremia to achieve undetectable HBV DNA. A recent multicenter European study estimated that the probability of achieving undetectable HBV DNA after 96 weeks of therapy with TDF was 63% among patients starting from a baseline viral load of $>10^8$ IU/mL, compared with 99% for those starting from a baseline viral load of $<10^5$ IU/mL.[24] The current study suggests that ETV combined with TDF may provide an incremental benefit in suppressing HBV replication among patients with a high baseline viral load but not in those with a low baseline viral load. Whether this difference is clinically relevant is unclear, but it is possible that a more rapid decline in HBV DNA replication may be important in patients who will be starting immunosuppressive therapy if their viral load is very high. A more rapid suppression of viral replication may also reduce the incidence of drug resistance. This has been shown in previous studies of lamivudine, telbivudine, and adefovir dipivoxil, which are NAs with a low genetic barrier to resistance.[25–27] In this study, low frequencies of virologic breakthrough were observed in both treatment arms throughout the study, with no evidence of HBV resistance development to ETV or TDF, suggesting that the few cases of virologic breakthrough may have been due

Table 3. Cumulative Safety Through Week 96

	No. of patients (%)	
	ETV (n = 182)	ETV + TDF (n = 197)
All adverse events	132 (72.5)	131 (66.5)
Serious adverse events	12 (6.6)	14 (7.1)
Injury, poisoning, and procedural complications	0	4 (2.0)
Infections and infestations	0	3 (1.5)
Gastrointestinal disorders	2 (1.1)	2 (1.0)
Neoplasms	3 (1.6)[a]	2 (1.0)[b]
Nervous system disorders	4 (2.2)	0
Miscellaneous causes	5 (2.7)	3 (1.5)
Discontinuation due to adverse event	2 (1.1)	5 (2.5)
ALT flares[c]		
On treatment	1 (0.5)	2 (1.0)
Off treatment	0	0
Increase in creatinine by ≥0.3 mg/dL	6 (3.3)	4 (2.0)
Increase in creatinine by ≥0.5 mg/dL	3 (1.6)	0
Malignancies[d]	4 (2.2)[e]	1 (0.5)[f]
Deaths[d]	0	3

NOTE. All events are on treatment unless stated otherwise. Deaths are reported for enrolled patients, and other parameters are reported for treated patients.

[a]2 hepatocellular carcinoma, 1 gastric cancer.

[b]1 breast cancer, 1 bile duct tumor.

[c]ALT level >2 times baseline and >10 times ULN.

[d]On-treatment and during postdosing follow-up.

[e]3 hepatocellular carcinoma, 1 gastric cancer.

[f]Breast cancer.

to nonadherence. The resistance rates observed in this study are consistent with those from previous studies with 96 weeks of ETV or TDF monotherapy.[9,14,28]

Combination therapy provided a benefit in a subset of HBeAg-positive patients over 96 weeks of therapy. However, long-term studies of ETV and TDF monotherapy showed that the vast majority of patients, even those with an initial partial virologic response, eventually achieved undetectable HBV DNA with a very low rate of resistance development.[8,12,13,16,17,29,30] Extension of the phase 3 trial of ETV (ETV 0.5 mg for 2 years in phase 3 studies, followed by up to 3 years of ETV 1.0 mg in a rollover study) showed that 94% of HBeAg-positive patients, with a baseline viral load of approximately 10^{10} IU/mL, achieved an HBV DNA level <300 copies/mL (~60 IU/mL) over 5 years,[8] and resistance to ETV was documented in only 1.2% of treated patients.[17] In another study of ETV, 76.5% of patients with a baseline HBV DNA level ≥8 $\log_{10}$ copies/mL (~7.3 $\log_{10}$ IU/mL) achieved an HBV DNA level <60 copies/mL (12 IU/mL) over 3 years of continuous ETV treatment (0.5 mg), with no evidence of resistance among those with detectable HBV DNA at week 24.[30] Likewise, continued treatment with TDF for up to 5 years resulted in 96%–99% of patients achieving undetectable serum HBV DNA, with no evidence of TDF resistance, although in the 51 patients with detectable HBV DNA at week 72, emtricitabine could be added to TDF, and 38 (75%) of the eligible patients chose to do so.[12,13,15,18]

In the subset of HBeAg-negative patients, both regimens showed comparable antiviral efficacy over 96 weeks of therapy. The difference in treatment outcome between HBeAg-negative and HBeAg-positive patients may be due to the lower viral load at baseline in HBeAg-negative patients (6.09 vs 8.15 $\log_{10}$ IU/mL).

Although combination therapy achieved higher rates of viral suppression in HBeAg-positive patients, it did not result in higher rates of HBeAg loss, HBeAg seroconversion, or ALT normalization. Similar observations have been made previously, showing that NAs with more potent viral suppression do not necessarily lead to higher rates of HBeAg seroconversion. For example, despite having superior antiviral efficacies, entecavir and tenofovir do not lead to higher rates of HBeAg seroconversion than lamivudine or adefovir.[9,11,31] Similarly, the combination of pegylated interferon and lamivudine results in a higher rate of virologic suppression, but not HBeAg loss or HBeAg seroconversion, than pegylated interferon alone.[32] The higher rate of ALT normalization with ETV alone may be due to the lower dropout rate in the monotherapy arm than in the combination therapy arm (7% vs 12%); however, the difference in the dropout rate was not statistically significant, and the difference in ALT normalization between the 2 treatment groups persisted when the analysis was limited to patients who remained in the study at week 96 (NC=M analysis; Supplementary Table 1). The reason for a higher rate of ALT normalization in the ETV monotherapy arm despite less marked viral suppression is unclear. One possible explanation may be related to lower baseline ALT levels in that group (127 vs 158 U/L). In that respect, the comparable rates of HBeAg seroconversion in both treatment arms were unexpected because previous studies of interferon and NA treatment showed that higher pretreatment ALT level was associated with a higher rate of HBeAg seroconversion.[33,34] Post hoc analyses of the current study also showed higher rates of HBeAg loss and HBeAg seroconversion in subgroups with higher baseline ALT levels; however, higher rates of HBeAg loss and HBeAg seroconversion were observed with ETV monotherapy compared with combination therapy even after stratification by baseline ALT level.

Rates of HBsAg loss and HBsAg seroconversion were low and comparable in both treatment groups. The serologic responses for both HBeAg and HBsAg that were observed in the ETV monotherapy arm of this study are consistent with previously reported serologic responses after 96 weeks of ETV treatment[9] and comparable to those reported for 144 weeks of TDF treatment.[14]

Both treatments were generally well tolerated and had comparable safety profiles. On-treatment ALT flares were infrequent and were associated in all cases with a decrease in HBV DNA level and subsequent HBeAg seroconversion. No apparent differences in serum creatinine elevations were detected between the 2 arms. Thus, through 96 weeks of therapy, the combination of ETV and TDF was not associated with increased risks of renal impairment or other adverse events. During the study, 5 malignancies

were diagnosed; of these, 3 were HCC. The 3 patients with HCC were diagnosed between 261 and 736 days after treatment initiation. All 3 patients had undetectable HBV DNA before diagnosis of HCC. HCC is a known complication of CHB, and it is possible that the tumors were present before the start of treatment.[35] Three deaths were reported throughout the duration of the study. Of these, one death was due to liver failure. Although this patient had virologic breakthrough and a probable acute hepatitis flare, resistance to ETV or TDF was not detected, suggesting that continued viremia may have been due to nonadherence.

One limitation of this study is the absence of a TDF monotherapy arm. However, in phase 3 studies of TDF, treatment over 2 years resulted in approximately 75% of HBeAg-positive patients and 90% of HBeAg-negative patients achieving an HBV DNA level <400 copies/mL,[14] which is comparable to the results observed with the combined therapy or ETV monotherapy in this study. Furthermore, the study is limited by the short duration of treatment; studies with a treatment duration of more than 2 years would be needed to assess the resistance rate and safety profile of the combination therapy during long-term use.[36]

In conclusion, this study shows that over 96 weeks of treatment, the antiviral efficacy of ETV monotherapy is similar to that of ETV plus TDF combination therapy in a mixed population of NA-naïve patients with CHB. Combination therapy was more effective than monotherapy in HBeAg-positive patients ($P = .046$), but this outcome was only observed in patients with a baseline HBV DNA level $\geq 10^8$ IU/mL. The safety profiles of the 2 treatments were comparable, with no evidence of increased renal or other toxicities with combination therapy. Frequencies of virologic breakthrough were comparable between both arms, and no resistance to either drug was observed. Evaluation of the combination of ETV plus TDF beyond 96 weeks is necessary to confirm its safety and efficacy during long-term use.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2012.05.037.

References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B. J Hepatol 2009;50:227–242.
2. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661–662.
3. Lok AS, Zoulim F, Locarnini S, et al. Antiviral drug-resistant HBV: standardization of nomenclature and assays and recommendations for management. Hepatology 2007;46:254–265.
4. Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA 2010;304:321–333.
5. Sung JJ, Lai JY, Zeuzem S, et al. Lamivudine compared with lamivudine and adefovir dipivoxil for the treatment of HBeAg-positive chronic hepatitis B. J Hepatol 2008;48:728–735.
6. Lai CL, Leung N, Teo EK, et al. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology 2005;129:528–536.
7. Woo G, Tomlinson G, Nishikawa Y, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. Gastroenterology 2010;139:1218–1229.
8. Chang TT, Lai CL, Kew YS, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. Hepatology 2010;51:422–430.
9. Gish RG, Lok AS, Chang TT, et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. Gastroenterology 2007;133:1437–1444.
10. Lai CL, Shouval D, Lok AS, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006;354:1011–1020.
11. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359:2442–2455.
12. Heathcote EJ, Gane EJ, de Man RA, et al. Long-term (4 year) efficacy and safety of tenofovir disoproxil fumarate (TDF) treatment in HBeAg-positive patients with chronic hepatitis B (study 103) (abstr 477). Hepatology 2010;52:556A.
13. Marcellin P, Buti M, Krastev Z, et al. Continued efficacy and safety through 4 years of tenofovir disproxil fumarate (TDF) treatment in HBeAg-negative patients with chronic hepatitis B (study 102) (abstr 476). Hepatology 2010;52:538A.
14. Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. Gastroenterology 2011;140:132–143.
15. Marcellin P, Buti M, Gane EJ, et al. Five years of treatment with tenofovir DF (TDF) for chronic hepatitis B (CHB) infection is associated with sustained viral suppression and significant regression of histological fibrosis and cirrhosis (abstr 1375). Hepatology 2011;54:1011A.
16. Snow-Lampart A, Chappell B, Curtis M, et al. No resistance to tenofovir disoproxil fumarate detected after up to 144 weeks of therapy in patients monoinfected with chronic hepatitis B virus. Hepatology 2011;53:763–773.
17. Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naive patients is rare through 5 years of therapy. Hepatology 2009;49:1503–1514.
18. Marcellin P, Heathcote EJ, Corsa A, et al. No detectable resistance to tenofovir disoproxil fumarate (TDF) following up to 240 weeks of treatment in patients with HBeAg+ and HBeAg- chronic hepatitis B virus infection (abstr 238). Hepatology 2011;54:480A.
19. Manns MP, Akarca US, Chang TT, et al. Long-term safety and tolerability of entecavir in patients with chronic hepatitis B in the rollover study ETV-901. Expert Opin Drug Saf 2012;11:361–368.
20. Mauss S, Berger F, Filmann N, et al. Effect of HBV polymerase inhibitors on renal function in patients with chronic hepatitis B. J Hepatol 2011;55:1235–1240.
21. Duarte-Rojo A, Heathcote EJ. Efficacy and safety of tenofovir disoproxil fumarate in patients with chronic hepatitis B. Therap Adv Gastroenterol 2010;3:107–119.
22. Lange CM, Bojunga J, Hofmann WP, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. Hepatology 2009;50:2001–2006.
23. Pawlotsky JM, Dusheiko G, Hatzakis A, et al. Virologic monitoring of hepatitis B virus therapy in clinical trials and practice: recommendations for a standardized approach. Gastroenterology 2008;134:405–415.

24. Lampertico P, Soffredini R, Viganò M, et al. 2-year effectiveness and safety of tenofovir in 302 NUC-naive patients with chronic hepatitis B: a multicenter European study in clinical practice (abstr 1433). Hepatology 2011;54(Suppl 1):1041A.
25. Zeuzem S, Gane E, Liaw YF, et al. Baseline characteristics and early on-treatment response predict the outcomes of 2 years of telbivudine treatment of chronic hepatitis B. J Hepatol 2009;51:11–20.
26. Fung SK, Andreone P, Han SH, et al. Adefovir-resistant hepatitis B can be associated with viral rebound and hepatic decompensation. J Hepatol 2005;43:937–943.
27. Yuen MF, Sablon E, Hui CK, et al. Factors associated with hepatitis B virus DNA breakthrough in patients receiving prolonged lamivudine therapy. Hepatology 2001;34:785–791.
28. Shouval D, Akarca U, Hatzis G. Continued virologic and biochemical improvement through 96 weeks of entecavir treatment In HBeAg(-) chronic hepatitis B patients (study ETV-027). Hepatology 2006;44(Suppl 2):S21.
29. Zoutendijk R, Reijnders JG, Brown A, et al. Entecavir treatment for chronic hepatitis B: Adaptation is not needed for the majority of naive patients with a partial virological response. Hepatology 2011;54:443–451.
30. Yuen MF, Seto WK, Fung J, et al. Three years of continuous entecavir therapy in treatment-naive chronic hepatitis B patients: viral suppression, viral resistance, and clinical safety. Am J Gastroenterol 2011;106:1264–1271.
31. Leung N, Peng CY, Hann HW, et al. Early hepatitis B virus DNA reduction in hepatitis B e antigen-positive patients with chronic hepatitis B: A randomized international study of entecavir versus adefovir. Hepatology 2009;49:72–79.
32. Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005;352:2682–2695.
33. Perrillo RP, Lai CL, Liaw YF, et al. Predictors of HBeAg loss after lamivudine treatment for chronic hepatitis B. Hepatology 2002; 36:186–194.
34. Buster EH, Hansen BE, Lau GK, et al. Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon-alfa. Gastroenterology 2009;137: 2002–2009.
35. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65–73.
36. Liaw YF, Sheen IS, Lee CM, et al. Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. Hepatology 2011;53: 62–72.

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Conflicts of interest

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Supplementary Table 1. Virologic, Biochemical, and Serologic Responses at Weeks 48 and 96

	ETV		ETV + TDF	
	Week 48	Week 96	Week 48	Week 96
HBV DNA <50 IU/mL, n/N (%)				
Overall	128/176 (72.7)	139/165 (84.2)	158/180 (87.8)	164/170 (96.5)
HBeAg positive	77/120 (64.2)	88/113 (77.9)	103/125 (82.4)	111/115 (96.5)
HBeAg negative	51/56 (91.1)	51/52 (98.1)	55/55 (100.0)	53/55 (96.4)
ALT normalization, n/N (%)				
Overall	151/176 (85.8)	149/168 (88.7)	143/183 (78.1)	136/173 (78.6)
HBeAg positive	102/120 (85.0)	103/115 (89.6)	97/126 (77.0)	89/117 (76.1)
HBeAg negative	49/56 (87.5)	46/53 (86.8)	46/57 (80.7)	47/56 (83.9)
HBeAg loss, n/N (%)[a]	32/119 (26.9)	49/113 (43.4)	27/127 (21.3)	41/113 (35.3)
HBeAg seroconversion n/N (%)[a]	28/119 (23.5)	41/113 (36.3)	25/127 (19.7)	30/116 (25.9)
HBsAg loss, n/N (%)				
Overall	4/175 (2.3)	5/166 (3.0)	2/182 (1.1)	7/171 (4.1)
HBeAg positive	4/119 (3.4)	5/114 (4.4)	2/126 (1.6)	7/116 (6.0)
HBeAg negative	0/56	0/52	0/56	0/55
HBsAg seroconversion, n/N (%)				
Overall	1/175 (0.6)	2/166 (1.2)	1/182 (0.5)	4/171 (2.3)
HBeAg positive	1/119 (0.8)	2/114 (1.8)	1/126 (0.8)	4/116 (3.4)
HBeAg negative	0/56	0/52	0/56	0/55

NOTE. Patients who discontinued study medication before week 96 were not counted as evaluable (NC=M).
[a]Among those HBeAg positive at baseline.