Research Article

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Efficacy of entecavir in treatment-naïve patients with hepatitis B virus-related decompensated cirrhosis

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Background & Aims: The effect of entecavir (ETV) therapy on viral suppression and hepatic function in hepatitis B virus (HBV) patients with decompensated cirrhosis has not been established. We evaluated ETV as first-line monotherapy in these patients.

Methods: We consecutively enrolled 70 HBV-infected patients with decompensated cirrhosis primarily treated with 0.5 mg/day ETV, and evaluated the clinical outcomes by intention-to-treat analyses. We also compared the virological responses of 55 patients treated for ⩾12 months (decompensated group) with those of 144 chronic hepatitis or compensated cirrhosis patients (compensated group).

Results: The cumulative transplantation-free survival was 87.1% at 1 year. ETV treatment for 12 months resulted in improved Child–Turcotte–Pugh (CTP) and model for end-stage liver disease (MELD) scores. Sixty-six percent (36/55) of patients achieved CTP class A and 49% (27/55) showed improvement in the CTP score of ⩾2 points after 12 months of ETV. The 1-year cumulative rates of HBV DNA negativity and HBeAg loss were 92.3% and 54.0%, respectively, by intention-to-treat analysis. The rates of HBV DNA negativity, HBeAg seroconversion/loss and ALT normalization at month 12 were similar for the decompensated and compensated groups. Cox regression analysis showed that pretreatment HBeAg seropositivity was a negative predictor of HBV DNA clearance during ETV therapy (hazard ratio, 0.514; 95% confidence interval 0.367–0.719; $p < 0.001$).

Conclusions: One-year initial ETV therapy was similarly effective in both compensated and decompensated liver disease HBV patients. In addition, it improved underlying liver function in decompensated patients.

Keywords: Entecavir; Efficacy; Hepatitis B virus; Decompensated cirrhosis.
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Abbreviations: HBV, hepatitis B virus; CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; LAM, lamivudine; ETV, entecavir; ALT, alanine aminotransferase; PT, prothrombin time; CTP score, Child–Turcotte–Pugh score; MELD score, model for end-stage liver disease; OLT, orthotopic liver transplantation.

Introduction

Approximately 15–40% of hepatitis B virus (HBV) carriers are at increased risk of serious sequelae such as cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC) [1,2]. In Korea, 5–7% of individuals within the general population are identified as HBV carriers [3], accounting for about 70% of liver cirrhosis and HCC cases [4]. The 5-year survival rate in decompensated cirrhosis patients is a low 14% compared with 84% for those with compensated cirrhosis [5].

A high viral load may be predictive of future progression to cirrhosis or HCC in HBV-infected patients [6,7]. The oral antiviral drug lamivudine (LAM) slows deterioration in chronic hepatitis B (CHB) and advanced liver disease patients by delaying hepatic decompensation and HCC development [8]. However, LAM is no longer considered an optimal first-line therapy in CHB patients, owing to its higher resistance rate and lower potency compared to entecavir (ETV) and telbivudine [9–12]. Latest recommendations suggest using ETV and tenofovir as primary oral agents irrespective of hepatitis B e antigen (HBeAg) serostatus [13].

ETV is considered an excellent treatment alternative for nucleos(t)ide-naïve patients due to insignificant resistance rates and strong antiviral effects [9,12], and is thus widely prescribed. In recent 48-week trials of ETV treatment for CHB, 67% of HBeAg-positive and 90% of HBeAg-negative patients showed HBV DNA reduction to undetectable levels [9,12], consistent with data obtained from patients with advanced liver fibrosis or compensated cirrhosis [14]. Furthermore, over 5 years of treatment, the cumulative probability of development of mutations in the virus conferring genotypic resistance to ETV was only 1.2% in nucleos(t)ide-naïve patients [15]. Hence, early ETV therapy may halt disease progression more effectively in chronically infected patients compared with LAM.

At present, limited information is available on the impact of ETV therapy on viral suppression and hepatic function in CHB patients, particularly those with decompensated cirrhosis. In

addition, the issue of when to use ETV as a first-line option in CHB therapy remains to be established.

In the present study, we evaluated the efficacy of ETV monotherapy in HBV-infected patients. We compared outcomes between decompensated cirrhosis patients and those with CHB or compensated cirrhosis. In addition, we investigated the effect of ETV therapy on hepatic function in patients with decompensated cirrhosis.

Patients and methods

Study population

From January 2007 to March 2008, 70 consecutive treatment-naive patients with HBV-related decompensated cirrhosis were orally treated with 0.5 mg/day ETV alone at our institution. Of these patients, 6 (8.6%) died during the follow-up period, and all deaths were due to hepatic failure within 6 months of ETV therapy (Fig. 1). Three patients (4.3%) underwent orthotopic liver transplantation (OLT) 3 or 4 months after the commencement of ETV therapy. At the time of OLT, all three had intractable ascites and/or grade 3 or 4 hepatic encephalopathy, with model for end-stage liver disease (MELD) score $\geqslant$15. Six patients (8.6%) were lost to follow-up before evaluation at 12 months, but were still alive. We analyzed clinical data from the remaining 55 patients with decompensated cirrhosis (decompensated group; Fig. 1), along with those from 144 consecutive patients with CHB or compensated cirrhosis (compensated group) who underwent 0.5 mg/day ETV treatment for at least 12 months during the same period. None of these patients had evidence of HCC at the time of initiation of ETV. CHB patients showing hepatic decompensation during acute exacerbation, defined as an elevation of alanine aminotransferase (ALT) activity to more than 10 times the upper limit of normal and more than twice the baseline value [16] were not included in the decompensated group. No patient had been previously administered antiviral therapy involving interferon-α or nucleos(t)ide analogs. All patients with or without HBeAg were persistently positive for hepatitis B surface antigen (HBsAg) for more than 6 months, and contained serum HBV DNA levels of 4 $\log_{10}$ copies/ml or greater at baseline. Patients displaying antibodies against hepatitis C (anti-HCV) or human immunodeficiency virus (anti-HIV) or who had undergone liver or other organ transplants were excluded.

Decompensated liver disease was established based on a Child–Turcotte–Pugh (CTP) score $\geqslant$ 7 (class B and C) or the presence of portal hypertension complications such as ascites, variceal bleeding or hepatic encephalopathy [17,18]. Liver cirrhosis was diagnosed based on clinical, radiological, or histological assessments. The study was approved by the institutional review board of our hospital.

Laboratory and radiological testing

Baseline serological and imaging data such as ultrasonography (USG) or spiral computed tomography (CT) were obtained for all subjects. Serum hepatitis viral markers, including HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HCV and anti-HIV, were confirmed using commercially available enzyme immunoassays (Abbott Laboratories, Chicago, IL). Serum HBV DNA levels were quantified using the Abbott Real-Time PCR assay (Abbott Laboratories, Chicago, IL) with a linear dynamic range of detection of 5.1×10^1–3.4×10^9 copies/ml, according to the manufacturer's instructions. Other laboratory parameters were assayed using standard analytical procedures.

Follow-up studies

Compensated and decompensated groups were followed-up every 3–6 months with tests for liver function, prothrombin time (PT), HBeAg, anti-HBe, and HBV DNA levels, in company with USG or spiral CT. Clinical examination and counseling regarding treatment adherence were performed for all patients at every clinic visit.

Statistical analysis

The two groups were compared using Student's *t*-test or Mann–Whitney test for continuous variables and chi-square or Fisher's exact test for categorized variables, where appropriate. Covariates with *p*-values < 0.20 in univariate analysis were included in multivariate analysis using Cox proportional hazards models to determine whether pretreatment clinical and laboratory variables were significant in predicting HBV DNA clearance during ETV treatment. A *p*-value < 0.05 was considered to indicate significance.

Results

Patient demographics

The baseline characteristics of the two study groups are shown in Table 1. The 199 total patients comprised 131 males and 68 females, and the gender ratio was similar for each group. The mean age was greater in the decompensated than the compensated group (52.6 vs. 46.8 years, $p < 0.001$). The two groups were similar in terms of serum HBV DNA levels. The mean serum ALT levels were lower in the decompensated group (101.9 vs. 156.5 IU/L, $p = 0.021$). The proportion of subjects positive for

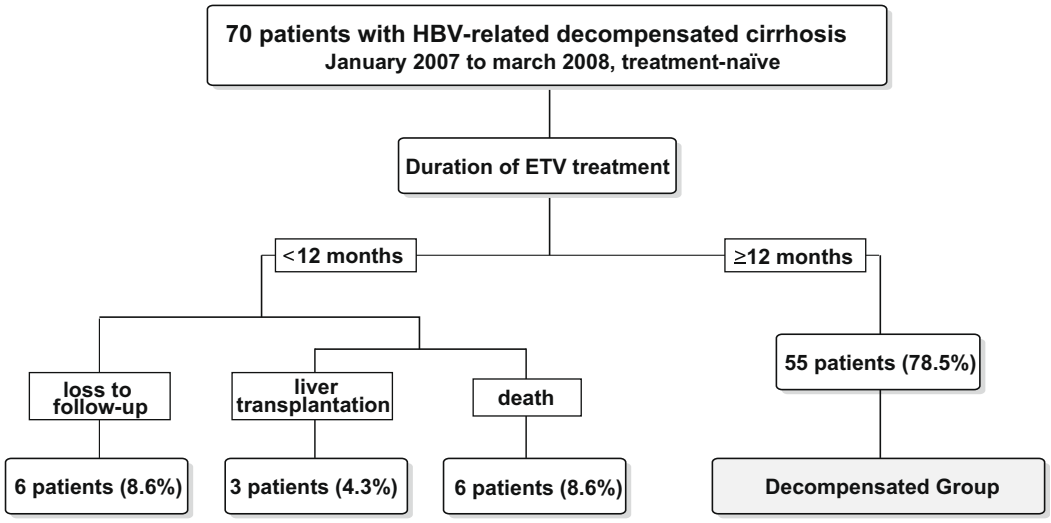

Fig. 1. Clinical outcomes in 70 treatment-naïve patients with HBV-related decompensated cirrhosis who were treated with 0.5 mg/day ETV.