Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Entecavir treatment in patients with severe acute exacerbation of chronic hepatitis B

Vincent Wai-Sun Wong, Grace Lai-Hung Wong, Karen Kar-Lum Yiu, Angel Mei-Ling Chim, Shirley Ho-Ting Chu, Hoi-Yun Chan, Joseph Jao-Yiu Sung, Henry Lik-Yuen Chan*

Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong; Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong

Background & Aims: Severe acute exacerbation of chronic hepatitis B is a unique clinical presentation with significant morbidity and mortality. Lamivudine was used in most previous studies, but the drug was limited by the development of resistance. Our objective is to study the safety and efficacy of entecavir in patients with severe acute exacerbation.

Methods: Consecutive patients with severe acute exacerbation of chronic hepatitis B were recruited from 1998 to 2009. All patients had serum alanine aminotransferase and bilirubin increased beyond 10 and 3 times the upper limit of normal, respectively. The primary endpoint was overall mortality at week 48. Virological and biochemical responses were also studied.

Results: Thirty-six patients and 117 patients were treated with entecavir and lamivudine, respectively. By week 48, 7 (19%) patients in the entecavir group and 5 (4%) patients in the lamivudine group died (adjusted hazard ratio 5.1, 95% confidence interval 1.5–17.2, $p = 0.010$). Similarly, the entecavir group had higher liver-related mortality (adjusted hazard ratio 4.0, 95% confidence interval 1.0–15.7, $p = 0.044$). Despite a lower prevalence of cirrhosis, more patients in the entecavir group developed prolonged jaundice, hepatic encephalopathy, and ascites. Entecavir resulted in more rapid and complete viral suppression, with 71% of patients achieving undetectable hepatitis B virus (HBV) DNA at week 48, compared to 40% in the lamivudine group ($p = 0.007$). However, rapid HBV DNA reduction at week 4 was associated with prolonged jaundice.

Conclusions: Entecavir treatment is associated with increased short-term mortality in patients with severe acute exacerbation of chronic hepatitis B but achieves better virological response in the long run.

Keywords: Antiviral agents; Entecavir; Lamivudine; Jaundice; Liver failure; Hepatic encephalopathy; Treatment outcome.

Received 29 April 2010; received in revised form 28 June 2010; accepted 29 June 2010; available online 7 September 2010

*Corresponding author. Address: Department of Medicine and Therapeutics, 9/F, Prince of Wales Hospital, 30–32 Ngan Shing Street, Shatin, Hong Kong. Tel.: +852 26323593; fax: +852 26373852.

E-mail address: hlychan@cuhk.edu.hk (H.Lik-Yuen Chan).

Abbreviations: ALT, alanine aminotransferase; Anti-HBe, antibody against hepatitis B e antigen; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; INR, international normalized ratio; ULN, upper limit of normal.

Introduction

It is estimated that over 350 million people worldwide are chronically infected with hepatitis B virus (HBV). Chronic hepatitis B is one of the most important causes of cirrhosis and hepatocellular carcinoma [1]. In some patients, spontaneous acute exacerbation of the disease occurs, which is characterized by very high serum alanine aminotransferase (ALT) level and jaundice. [2] This may progress to acute-on chronic liver failure and death [3].

Owing to the high morbidity and mortality, most guidelines recommend oral nucleoside analogs in patients with severe acute exacerbation of chronic hepatitis B [4,5]. For historical reasons, most observational studies reported the experience of using lamivudine in this situation [6–8]. However, lamivudine is associated with a high risk of drug resistance and virological breakthrough [9]. Although drug resistance appears to be less common in patients with severe acute exacerbation of chronic hepatitis B, the cumulative incidence of lamivudine resistance remains substantial at 25% in 4 years, in patients with hepatitis B e antigen (HBeAg)-negative disease and 33% in 5 years, in patients with HBeAg-positive disease [6,7]. Lamivudine resistance also results in significant biochemical breakthrough and liver decompensation in some cases [7]. A better treatment with a lower risk of virological breakthrough is preferred.

Entecavir is another oral nucleoside analog with potent antiviral activity [10,11]. In treatment-naïve patients, the incidence of genotypic resistance to entecavir is only 1.2% at 5 years [12]. While there is little doubt that entecavir is associated with a lower rate of resistance in the long run, its safety during severe acute exacerbation of chronic hepatitis B is unknown. In a recent report of 16 decompensated cirrhotic patients treated with entecavir, five developed severe lactic acidosis and one of them died [13]. Safety data in different groups of patients are, therefore, urgently needed.

In this study, we aimed to investigate the safety of entecavir in patients with severe acute exacerbation of chronic hepatitis B. The clinical outcomes were compared to historical controls who received lamivudine.

Patients and methods

Consecutive patients, admitted to the Prince of Wales Hospital, Hong Kong with spontaneous severe acute exacerbation of chronic hepatitis B, were prospectively studied. Severe acute exacerbation of chronic hepatitis B was defined as elevation

of ALT to more than 10 times the upper limit of normal (ULN, 58 IU/L) and bilirubin to at least three times ULN (15 μmol/L). All patients had positive hepatitis B surface antigen (HBsAg) for more than 6 months. Coinfection by hepatitis A virus, hepatitis C virus, and hepatitis E virus was excluded by serological assays. Abdominal ultrasound was performed during admission to exclude hepatocellular carcinoma and biliary obstruction. All patients were antiviral treatment-naïve. No patient had hepatic encephalopathy, ascites or abnormal renal function test at baseline. Patients who received immunosuppressants or systemic corticosteroids were also excluded. Cirrhosis by ultrasound was defined as coarse liver echotexture with nodularity and small liver size and the presence of features of portal hypertension (e.g. ascites, splenomegaly and varices).

From September 1998 to November 2007, patients fulfilling the same inclusion and exclusion criteria received lamivudine 100 mg daily and served as historical controls. Entecavir was available in Hong Kong since November 2007 and became a reimbursable item from the hospital in July 2008 [14]. Therefore, entecavir 0.5 mg daily was prescribed to all patients on admission since November 2007. All patients were followed up at weeks 1, 2, 4, 8, 12, and then every 3 months to monitor serum liver biochemistry. Hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe) were monitored every 6 months and HBsAg was checked yearly. HBV DNA was checked at baseline, week 4, and then every 6 months.

Laboratory tests

HBsAg was tested using commercially available enzyme-linked immunosorbant assay kits (COBAS CORE HBsAg IIEIA, Roche Diagnostics Corporation, Indianapolis, IN, USA) and confirmed by neutralization assay. HBeAg and anti-HBe were measured by enzyme-linked immunosorbant assay (Sanofi Diagnostics, Pasteur, France). HBV DNA was measured by TaqMan real-time polymerase chain reaction using Eurohep standard.[15] The range of HBV DNA detection was 10^2 to 10^9 copies/ml.

Clinical endpoints

The primary endpoint was overall mortality at 48 weeks. Secondary endpoints included 30-day mortality, liver-related mortality at 48 weeks, liver-related complications (variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, ascites and spontaneous bacterial peritonitis), and duration of hospital stay. Efficacy endpoints included ALT normalization, bilirubin normalization, HBV DNA suppression to below 100 copies/ml, and HBeAg seroconversion in patients with positive HBeAg at baseline.

Statistical analysis

Statistical tests were performed by SPSS (version 16.0, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation or median (range). HBV DNA was logarithmic transformed to normal distribution for analysis. Negative HBV DNA was taken as 100 copies/ml for calculation. Continuous variables were compared by Student's *t* test or Mann–Whitney *U* test. Categorical variables were compared by χ^2 test or Fisher exact test as appropriate. The time to death or to the last follow-up was plotted according to the treatment groups by Kaplan–Meier estimates and compared by using the log-rank test. Baseline was taken as the date when the first dose of entecavir or lamivudine was taken. Cox-proportional hazard model was used to adjust for baseline variables. Statistical significance was taken as a two-sided *p* value <0.05.

Results

Thirty-six patients who fulfilled the inclusion and exclusion criteria received entecavir treatment. One hundred and seventeen patients who received lamivudine served as historical controls. The follow-up duration of the entecavir and lamivudine groups was 74 ± 52 and 316 ± 143 weeks, respectively (p <0.001). Patients in the entecavir group were older but had lower baseline ALT level (Table 1). There were more female patients in the entecavir group. Otherwise, the baseline bilirubin, albumin, international normalized ratio (INR), and platelet count at the time of commencing antiviral therapy were similar between the groups. Fewer patients in the entecavir group had cirrhosis, though the difference did not reach statistical significance.

Mortality and liver-related complications

By week 48, 7 (19%) patients in the entecavir group and 5 (4%) patients in the lamivudine group died (Fig. 1A, p = 0.002 by log-rank test). Compared to the lamivudine group, the hazard ratio of overall mortality was 5.0 in the entecavir group (95% confidence interval, 1.6–15.7; p = 0.006). The difference in mortality was observed in the first 30 days, while the mortality rate between day 30 and week 48 was similar in the two groups (Table 2). One patient in each group subsequently died of other malignancies (carcinoma of pancreas in a patient on entecavir and acute myeloid leukemia in a patient on lamivudine) (Table 3). When only liver-related mortality was considered, the incidence remained significantly higher in the entecavir group (Fig. 1B, p = 0.004 by log-rank test). Compared to the lamivudine group,

Table 1. Baseline characteristics of patients with severe acute exacerbation of chronic hepatitis B on entecavir and lamivudine treatment.

Characteristics	Entecavir (N = 36)	Lamivudine (N = 117)	*p* Value
Age	51 ± 13 (22-76)	44 ± 14 (16-79)	0.005
Male gender, n (%)	26 (72)	101 (86)	0.049
ALT (IU/L)	1151 ± 724 (194-3020)	1499 ± 841 (181-5430)	0.027
Bilirubin (μmol/L)	165 ± 163 (23-754)	163 ± 121 (27-572)	0.94
Albumin (g/L)	36 ± 5 (22-47)	34 ± 5 (18-48)	0.29
Creatinine (μmol/L)	86 ± 31 (55-214)	90 ± 50 (37-558)	0.73
INR	1.58 ± 0.74 (1.03-4.15)	1.59 ± 0.43 (0.97-3.19)	0.95
Platelet count (×10^9/L)	174 ± 89 (35-425)	144 ± 57 (17-303)	0.071
HBeAg positive, n (%)	13 (36)	55 (47)	0.25
Anti-HBe positive, n (%)	20 (56)	52 (44)	0.24
HBV DNA (log copies/ml)	7.29 ± 2.08 (2.00-11.33)	7.56 ± 1.62 (2.00-10.30)	0.42
Cirrhosis, n (%)	5 (14)	25 (21)	0.32
Time from presentation to starting antiviral drugs (days)	2.9 ± 2.8 (0-9)	2.8 ± 4.1 (0-29)	0.90

Continuous variables were presented as mean ± standard deviation. The range was shown in brackets. Baseline characteristics referred to the day when antiviral therapy was commenced.
ALT, alanine aminotransferase; anti-Hbe, antibody against HbeAg; HbeAg, hepatitis B e antigen, HBV, hepatitis B virus; INR, international normalized ratio.