Original article

The ultra-short virological dynamics in response to entecavir or lamivudine during chronic hepatitis B with spontaneous severe acute exacerbation

*Teng-Yu Lee[1,2], Chi-Yi Chen[3], Hsueh-Chou Lia[4,5], Yu-Chung Hsu[6], Sheng-Shun Yang[1,7]**

[1]Division of Gastroenterology & Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan
[2]Department of Medicine, Chung Shan Medical University, Taichung, Taiwan
[3]Division of Gastroenterology & Hepatology, Chia-Yi Christian Hospital, Chia-Yi, Taiwan
[4]Division of Gastroenterology & Hepatology, China Medical University Hospital, Taichung, Taiwan
[5]School of Chinese Medicine, China Medical University, Taichung, Taiwan
[6]Center for Gastroenterology, Changhua Christian Hospital, Changhua, Taiwan
[7]Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan

*Corresponding author e-mail: yansh@vghtc.gov.tw

Background: Nucleoside/nucleotide analogue (NA) therapy could be life-saving in chronic hepatitis B (CHB) with spontaneous severe acute exacerbation (SAE). We aimed to investigate the ultra-short virological responses to NA.

Methods: We conducted a randomized controlled trial in which CHB patients with spontaneous SAE were randomized to receive lamivudine (LVD) or entecavir (ETV) between July 2012 and April 2016 (ClinicalTrials.gov: NCT01627223). The serum HBV viral loads on day 1 (baseline), 3, 5, 8, 15, 22, 29, 85 and 180 after initiating NA therapy were checked and analysed.

Results: In total, 17 patients (7 in LVD and 10 in ETV group) were recruited, and 3 patients (17.7%) died or received liver transplantation due to hepatic failure. The median (IQR) HBV DNA decline on days 3, 5, 8, 15, 22, 29, 85 and 180 were 1.38 (1.09–1.50), 2.36 (1.89–2.58), 3.19 (2.21–3.51), 3.76 (2.54–4.40), 3.43 (2.44–4.75), 4.00 (3.01–5.04), 5.00 (3.61–6.21) and 6.50 (4.12–7.20) log IU/ml, respectively. The baseline characteristics were basically similar between the two groups, and the dynamic changes in HBV DNA were not significantly different between the two groups. Further analysis of the patients with high HBV viral load (>6 log IU/ml) revealed that a similar baseline HBV DNA level in the two groups (LVD versus ETV: median 8.0 [7.5–8.8] versus 7.7 [6.6–8.4] log IU/ml; *P*=0.45), and the dynamic changes of HBV DNA were very similar.

Conclusions: CHB with spontaneous SAE responded similarly to treatment using either LVD or ETV, with both drugs inducing a rapid decline of HBV viral load.

Introduction

Chronic hepatitis B (CHB) with spontaneous acute exacerbation, characterized by an abrupt flare of serum HBV and alanine aminotransferase (ALT), is not uncommon among HBV carriers, with a cumulative incidence of 10–30% every year [1–3]. Severe acute exacerbation (SAE) is a severe form of hepatitis flare, which results in hepatic decompensation, hepatic failure and even death. The mortality rate of CHB with spontaneous SAE ranged from 12% to 98% [3,4]. Nucleoside/nucleotide analogues (NA) can directly inhibit HBV replication, and long-term NA therapy can effectively normalize serum ALT, improve liver histology and prevent liver decompensation [5]. However, in previous retrospective studies of CHB with spontaneous SAE, patient mortality might not be significantly reduced by the administration of NA, and therefore the role of NA therapy still needs to be defined [6,7]. A prospective study of NA therapy for CHB with spontaneous SAE is thus imperative.

Despite the limited published evidence to date, NA therapy is currently the most widely recommended treatment for CHB with spontaneous SAE [5,8,9]. Early awareness of hepatitis flare and urgent antiviral treatment with NAs may help improve patient survival [10]. However, hepatitis B flare may be abrupt and fulminant, and a proportion of patients may have already

suffered hepatic decompensation by the time they visit a clinician [4,11]. In two retrospective cohort studies using lamivudine (LVD) to treat CHB with spontaneous SAE, the authors reported that NA therapy might be ineffective once severe liver decompensation had developed, for example, serum bilirubin >20 mg/dl or Model for End-Stage Liver Disease score >30 [4,11]. For CHB patients who have suffered from SAE, the speed of virus suppression after initiating NA therapy may be an important prognostic factor and should be further investigated. However, there are sparse data on this issue in the literature.

Several NAs have been launched for the treatment of CHB, but the ability of these drugs to induce viral suppression may vary over time [12]. With the advantages of potent HBV suppression and a low drug resistance rate, a newer-generation NA, that is, entecavir (ETV) or tenofovir (TDF), has been recommended as the preferred choice for the long-term treatment of CHB [5,8,9]. However, compared to LVD therapy for treating CHB with spontaneous SAE, ETV surprisingly did not result in a better patient survival rate in retrospective investigations [13,14], and ETV was even reported to independently increase short-term mortality [15,16]. The reasons for the discrepancy in treatment outcome between general CHB and CHB with SAE are unclear. To date, no randomized controlled trials (RCT) have been conducted to compare different NAs in the treatment of CHB with SAE. Moreover, there are few data in the literature regarding the speed of HBV suppression in different NAs which may shed light on the possible mechanisms related to treatment outcomes. We thus conducted an RCT to investigate the ultra-short virological dynamics in response to ETV or LVD during CHB with spontaneous SAE.

Methods

Study design

This was a randomized, open-label, multicentre, Phase IV study (ClinicalTrials.gov: NCT01627223) to compare the short-term treatment responses to LVD or ETV in CHB patients with spontaneous SAE. All authors of this study had access to the study data and had reviewed and approved the final manuscript.

Using a central, interactive online computer response system, eligible patients were randomized (1:1) to LVD 100 mg (Zeffix®; GlaxoSmithKline, Ware, UK) or ETV 0.5 mg (Baraclude®; Bristol-Myers Squibb, Mount Vernon, IN, USA) at their first visit to our clinic. This randomization process was stratified by prolonged prothrombin time (PT) <4 s, 4–6 s and >6 s. After randomization, all patients immediately began taking their randomly assigned drug, LVD or ETV, orally every day with day 1 serving as the baseline.

In compliance with the Declaration of Helsinki, this study was approved independently by the Institutional Review Board of each investigator's hospital prior to commencement of the study initiation. The study was explained in detail to each participant in person. Informed consent was obtained from all study subjects before patient enrolment. The original target sample size was 74 patients, but this study was terminated early due to a delay in patient recruitment and the lack of a significant difference in the response to treatment between the two groups.

Study patients

Patients with CHB and spontaneous SAE were recruited as study candidates between July 2012 and April 2016. The inclusion criteria of study subjects were as follows: male or female ≥20 years of age; positive hepatitis B surface antigen (HBsAg) for at least 6 months or negative anti-HBc IgM; HBV DNA ≥2,000 IU/ml (note that a blood sample was collected at the screening visit, but this criterion was retrospectively checked after obtaining the laboratory result. Patients who fulfilled all other criteria were enrolled immediately); serum total bilirubin ≥2 mg/dl and/or prolonged prothrombin time (PT) ≥3 s; serum ALT ≥10× upper limit of normal (ULN); serum creatinine ≤1.5 ULN or calculated creatinine clearance ≥50 ml/min; willing and able to sign the written informed consent form.

The exclusion criteria of study subjects were as follows: patient who is pregnant or lactating; underlying liver cirrhosis classified as Child–Pugh class B or C before the current SAE episode; HAV, HCV, HDV or HIV coinfection; uncontrolled malignancy; history or presence of alcohol or substance abuse within 1 year prior to the study initiation; history of hypersensitivity to any of the ingredients contained in the studied drugs (LVD or ETV); current use of medicine which might induce hepatotoxicity; use of any antiviral therapy for HBV, such as interferon-α or NAs, within 6 months prior to commencement of the study; exposure to any antiviral treatment for more than 3 months; use of any chemotherapy or immunosuppressive agents within 12 months prior to the beginning of the study; use of any investigational product, including drugs and invasive medical devices, within 4 weeks prior to the beginning of the study; any medical or psychiatric conditions, including the presence of significant abnormal laboratory values, which were deemed to be unsuitable for inclusion in this study by the investigators.

Outcome measurement

Clinical data and blood samples were routinely collected on day 1 (baseline), 3, 5, 8, 15, 22, 29, 85 and 180 after initiating ETV or LVD, and overall survival and changes of HBV DNA during the study period were measured

and served as the study outcomes. In addition to biochemical data, which were used to evaluate liver function, virological data, such as hepatitis B e antigen (HBeAg), anti-HBe, HBV viral load (HBV DNA) and HBV genotype, were examined at baseline. Serum HBV DNA was checked by polymerase chain reaction (Roche COBAS TaqMan HPS assay; Roche Diagnostics, Indianapolis, IN, USA; lower limit of quantification: 29 IU/ml; upper limit of quantification: 1.1 log 8 IU/ml) in the central lab. If HBV DNA level was initially examined to be over the upper limit of quantification, a detailed HBV DNA level would be quantified using the dilution method. Changes in liver function parameters and serum HBV DNA were recorded to compare responses between the two groups. Patients were followed up until 180 days after NA initiation, mortality or receiving liver transplantation due to hepatic failure.

Statistical analysis

Categorical variables of demographic data were presented as case numbers along with their percentages (%) and they were compared using the χ^2 test or Fisher's exact test. Continuous variables of demographic data were presented as mean value ± standard deviation and median values (25–75% IQRs), respectively. HBV DNA was logarithmically transformed for analysis. The parameters for HBV kinetics were estimated with a general form of the viral kinetics equation [17,18], and they were estimated by the 'fminunc' function in GNU Octave 4.2.1. Viral clearance rate per day (c), infected cell loss rate per day (δ) and efficiency factor of blocking virus production (ε) were calculated for each patient. The mean and median values of continuous variables were compared using the Student's t-test and Mann–Whitney U test, respectively. Incidence rates of patient mortality and liver transplantation during the study period were calculated and presented as total number and percentage. Changes in liver function parameters and HBV DNA during the study period were presented as mean ± standard error, and differences between the LVD and ETV groups were compared by Student's t-test. Two-sided P-value <0.05 was considered to be statistically significant. Regression analyses were conducted to determine independent factors for undetectable HBV DNA at year 1 or transplantation-free survival. Odds ratios and hazard ratios were determined by logistic regression model and Cox proportional hazard model, respectively. Data were managed and analyzed using SAS 9.3 software (SAS Institute, Inc., Cary, NC, USA).

Results

Study subjects

There was a relatively low incidence of spontaneous SAE among CHB patients and most potential study candidates had received NA prescription at local clinics before referral to our medical centres. Therefore, patient recruitment in this study was delayed. A total of 17 patients (7 in the LVD group and 10 in the ETV group) were finally enrolled in this study. A detailed summary of the data is presented in Additional file 1. In this study, most patients were young to middle-aged with a median age of 39 years (range 27–77 years) and 76.5% of the patients were male. Around one-third of patients were positive for HBeAg, and nearly 90% of patients were infected with genotype B HBV. The degree of hepatitis flare was severe in all study subjects. The median (IQR) levels of serum HBV DNA, ALT, total bilirubin and prothrombin time (PT) were 7.7 (6.2–8.2) IU/ml, 1,766.0 (1,110.0–2,832.0) U/l, 4.5 (2.9–8.0) mg/dl and 1.4 (1.2–1.8) international normalized ratio (INR), respectively. In contrast, the median levels of albumin and creatinine were normal.

As shown in Table 1, the baseline characteristics of the study subjects in the LVD or ETV groups were

Table 1. Baseline characteristics of the study subjects in the lamivudine and entecavir groups

Characteristics	Lamivudine group (n=7)	Entecavir group (n=10)
Age, years		
Mean ±SD	42.7 ±16.5	44.6 ±13.0
Median (IQR)	35.0 (33.0–46.0)	43.5 (36.3–53.5)
Sex		
Male, *n* (%)	4 (57.1)	9 (90.0)
Female, *n* (%)	3 (42.9)	1 (10.0)
Positive HBeAg, *n* (%)	2 (28.6)	3 (30.0)
Positive anti-HBe, *n* (%)	5 (71.4)	7 (70.0)
HBV genotype		
B, *n* (%)	5 (71.4)	10 (100.0)
Non-B, *n* (%)	2 (28.6)	0 (0)
HBV DNA, log IU/ml		
Mean ±SD	8.3 ±1.4	6.5 ±1.7
Median (IQR)	8.0 (7.5–8.8)	6.2 (5.2–7.7)
ALT, U/l		
Mean ±SD	2,105.1 ±989.2	2,063.5 ±1,218.7
Median (IQR)	1,766.0 (1,393.0–2,814.5)	1,886.0 (1,195.5–2,766.8)
Bilirubin-total, mg/dl		
Mean ±SD	4.9 ±2.4	6.5 ±5.1
Median (IQR)	4.5 (3.3–6.4)	4.1 (2.9–8.4)
Prothrombin time, INR		
Mean ±SD	1.5 ±0.4	1.6 ±0.6
Median (IQR)	1.4 (1.2–1.6)	1.4 (1.2–1.7)
Albumin, g/dl		
Mean ±SD	3.6 ±0.6	3.3 ±1.2
Median (IQR)	3.4 (3.1–4.0)	3.7 (3.4–4.0)
Creatinine, mg/dl		
Mean ±SD	0.8 ±0.12	0.9 ±0.3
Median (IQR)	0.7 (0.7–0.9)	0.8 (0.7–1.0)

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; INR, international normalized ratio.

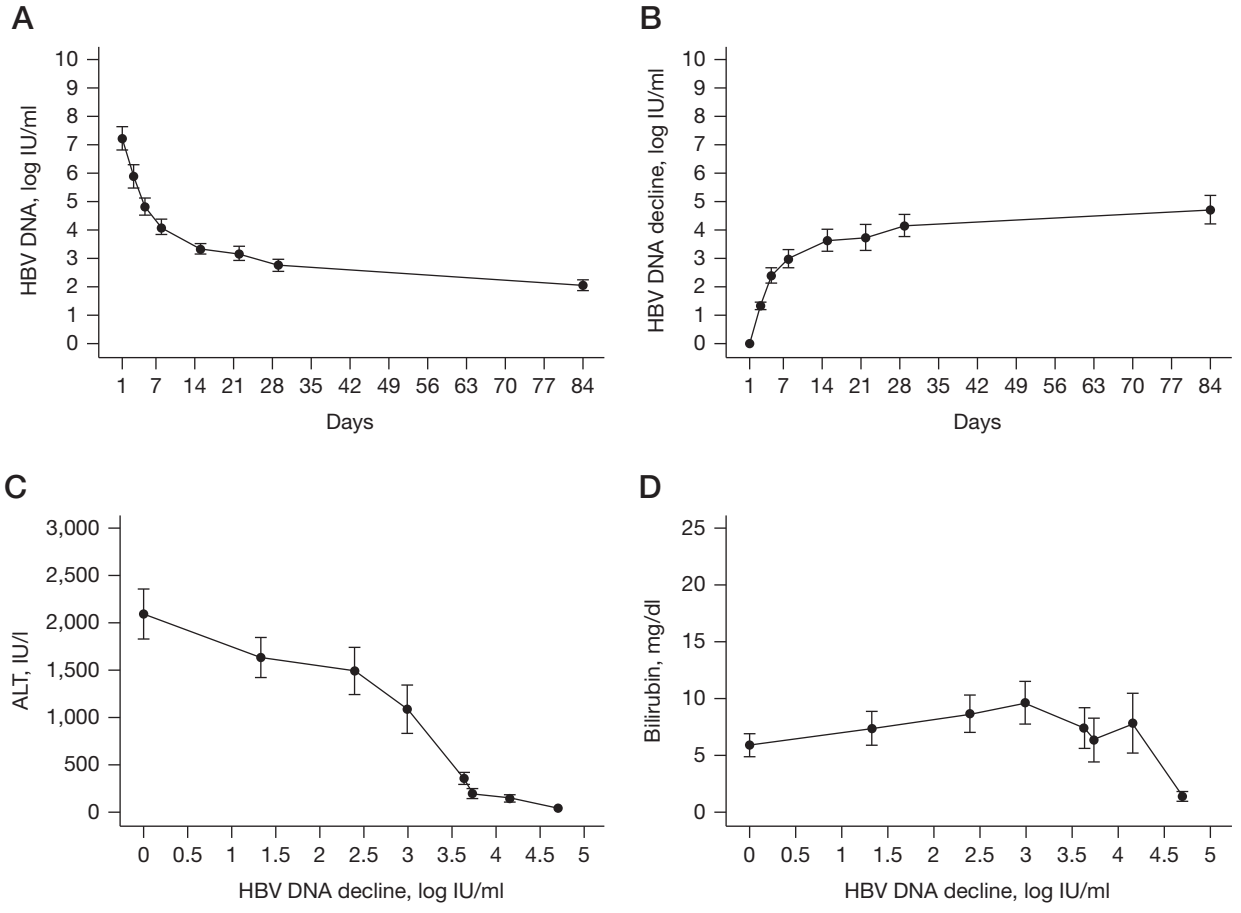
similar in age, sex, HBeAg positivity, anti-HBe-positivity, HBV genotype, ALT, total bilirubin, PT, albumin and creatinine. However, the levels of HBV DNA in the LVD group were higher than those in the ETV group (mean: 8.3 ±1.4 versus 6.5 ±1.7 log IU/ml; *P*=0.03; median [IQR]: 8.0 [7.5–8.8] versus 6.2 [5.2–7.7]; *P*=0.06) despite the random assignment of patients to the two groups at the beginning of the study. We further analysed patients with high viral loads (HBV DNA >6 log IU/ml) and all the baseline characteristics of the study subjects in the two groups were similar, including the level of HBV DNA (Additional file 2).

Measured outcomes in the study subjects

The outcomes of all study subjects were measured periodically over 180 days (Additional file 3). In total, three patients (17.7%) died or received liver transplantation due to hepatic failure. Compared with baseline, the median (IQR) levels of HBV DNA decline on days 3, 5, 8, 15, 22, 29, 85 and 180 were 1.38 (1.09–1.50), 2.36 (1.89–2.58), 3.19 (2.21–3.51), 3.76 (2.54–4.40), 3.43 (2.44–4.75), 4.00 (3.01–5.04), 5.00 (3.61–6.21) and 6.50 (4.12–7.20) IU/ml, respectively. HBV viral load was rapidly reduced by the NA therapy in this study (Figure 1A & 1B). In addition, significant ALT flare was not found during the rapid HBV DNA decline (Figure 1C). However, bilirubin usually remained elevated even after HBV DNA decline (to the peak at the first week after initiating NA therapy) and jaundice could persist for more than 1 month (Figure 1D).

Additional file 4 shows that the transplantation-free overall survival rates were not significantly different

Figure 1. The dynamic changes of HBV DNA, HBV DNA decline, ALT–HBV DNA decline, total bilirubin–HBV DNA decline in all study subjects



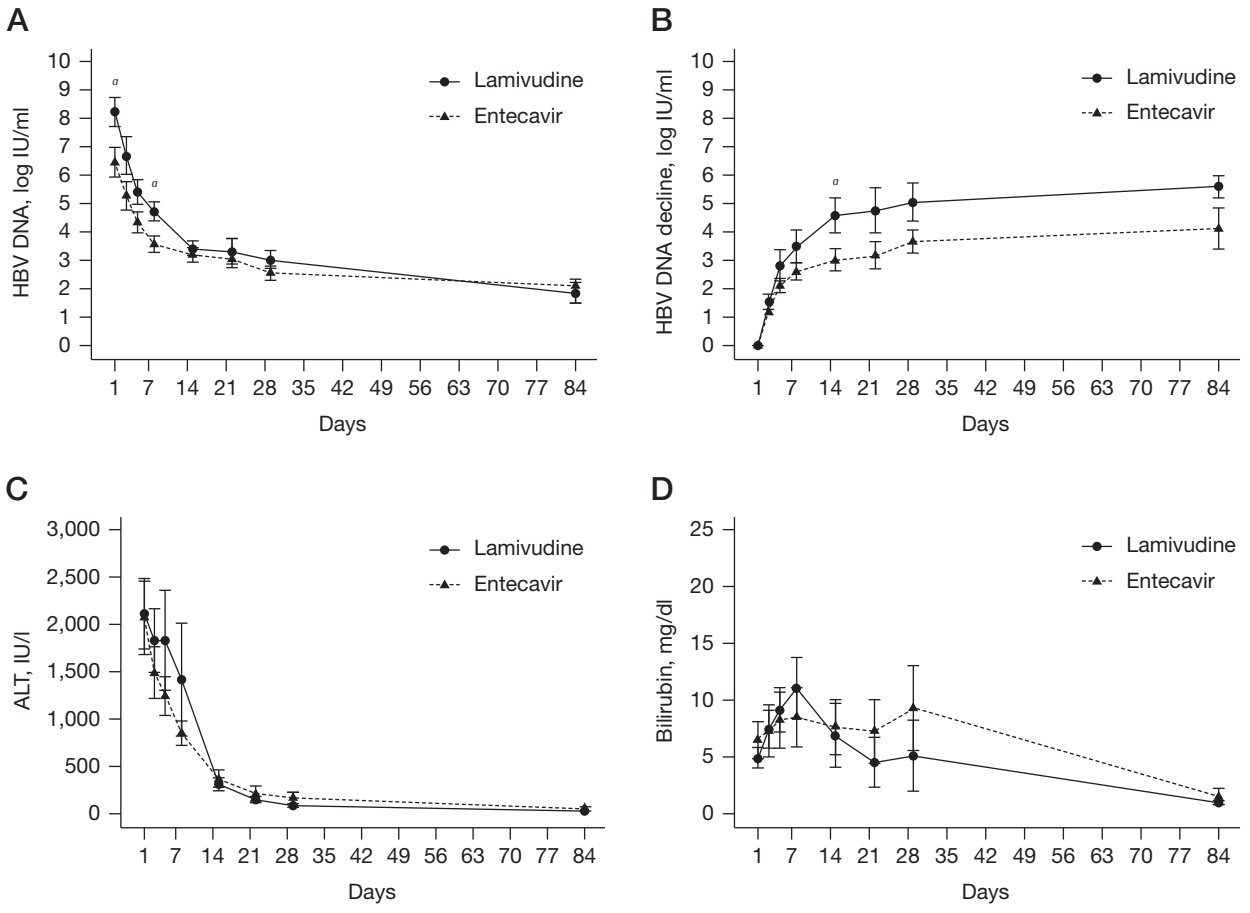
(A) HBV DNA, **(B)** HBV DNA decline, **(C)** alanine aminotransferase (ALT)–HBV DNA decline and **(D)** total bilirubin–HBV DNA decline in all study subjects. The data are presented as mean ± standard error.

between the two groups (P=1.00). There was a higher baseline serum HBV DNA level in the LVD group, but the decline of HBV DNA after initiating NA therapy was not significantly faster in the LVD group than that in the ETV group, except on day 15. Similarly, as shown in Figure 2A & 2B, the dynamic changes of HBV DNA and the degrees of HBV DNA decline during the study period were not significantly different, except on day 15. Other parameters of viral kinetics were also similar. In addition, as shown in Figure 2C & 2D, the dynamic changes of ALT and total bilirubin during the study were not significantly different. Furthermore, we analysed the ultra-short virological responses to find a predictor for transplantation-free overall survival in Additional file 5, but no prognostic factor was disclosed in regression analysis.

Measured outcomes in the study subjects with high serum viral loads

As presented in Additional file 6, among patients with serum HBV DNA >6 log IU/ml, the transplantation-free overall survival rates were not significantly different between the two groups (P=0.88). The two groups had a similar baseline serum HBV DNA level, and the decline of HBV DNA after initiating NA therapy was not significantly different between the two groups. Other parameters of viral kinetics were also similar. Moreover, as shown in Figure 3A & 3B, the dynamic changes of HBV DNA and extent of viral load decline during the study period were very similar in the two groups, and the median viral load decline was >3.0 log IU/ml in the first week. Furthermore, the ALT declines were very similar between the two groups (Additional file 6).

Figure 2. The dynamic changes of HBV DNA, HBV DNA decline, ALT and total bilirubin in the lamivudine and entecavir groups



(A) HBV DNA, **(B)** HBV DNA decline, **(C)** alanine aminotransferase (ALT) and **(D)** total bilirubin in the lamivudine and entecavir groups. The data are presented as mean ± standard error. [a]P<0.05.

Virological responses at year one

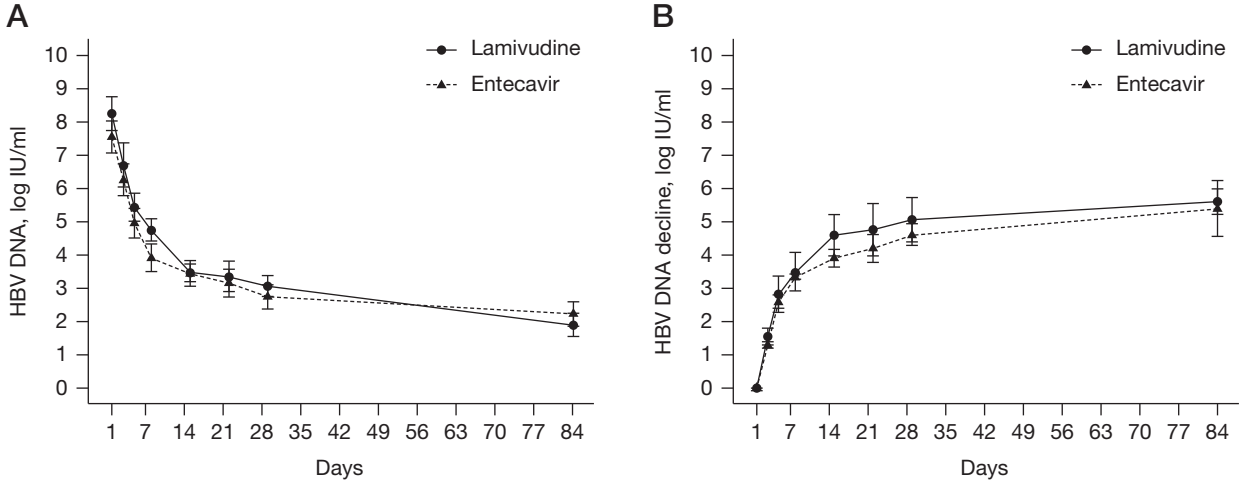
Except 3 patients who died or received liver transplantation and 2 patients who were lost to follow-up, the 1-year virological responses could be accessed for the remaining 12 patients (5 LVD and 7 ETV users). As undetectability of serum HBV DNA (virological response) was defined as a level less than the lower limit of quantification, the 1-year virological response rate was 66.7% in total. Comparing LVD users to ETV users, the 1-year virological response rates were not significantly different (80.0% versus 57.1%; P=0.84). Furthermore, as shown in Additional file 5, we analysed the ultra-short virological responses to find a predictor for 1-year virological response, but no outcome predictor was disclosed in regression analysis. In addition, as drug resistance was defined as a 10-fold increase of serum HBV DNA levels, no drug resistance to LVD or ETV was detected in 1 year.

Discussion

The dynamic changes of serum HBV DNA during CHB with spontaneous SAE have rarely been investigated, and to date no prospective studies have been conducted to compare the speed of virological suppression in different NAs. To the best of our knowledge, this is the first study to report the detailed virological changes within the first weeks after initiating NA therapy for CHB with spontaneous SAE. This clinical study clearly demonstrated that the decline of HBV viral load was very fast using either LVD or ETV, with a median HBV decline of >3 log IU/ml in the first week. The results of this study thus provide important evidence explaining why newer-generation NAs, that is, ETV, did not result in better survival benefit during CHB with spontaneous SAE compared to that of first-generation NA [13,14]. A large-scale RCT is needed to confirm our findings.

Even under NA therapy, the mortality rate among CHB patients with spontaneous SAE remains unsatisfactory and should be further improved [3,4]. In a clinical trial which randomly assigned patients to receive either TDF or placebo, the 3-month survival rate was significantly higher in the TDF than in the placebo group (57% versus 15%, respectively), and the reduction in serum HBV DNA >2 log at 2 weeks was found to be an independent prognostic predictor [19]. Although early awareness and urgent NA treatment may reduce the mortality rate [10], the speed of HBV suppression after initiating NA therapy may be an important prognostic factor. Current data shows that the newer-generation NAs have a more potent inhibitory effect on HBV after 1 year of use [9], but whether they provide faster virus suppression in CHB with spontaneous SAE has yet to be definitively established. However, our findings do not indicate that ETV should be selected over LVD, and ETV or LVD were found to be equally fast in terms of their ability to induce short-term HBV suppression. As rapid HBV suppression during SAE is a vital component of treatment, initiating NA therapy as soon as possible is more important than determining the optimal NA.

Figure 3. The dynamic changes of HBV DNA, HBV DNA decline among patients with high viral loads in the lamivudine and entecavir groups



(A) HBV DNA and **(B)** HBV DNA decline among patients with high viral loads in the lamivudine and entecavir groups. The data are presented as mean ± standard error.

Previous studies on viral kinetics after initiating NA therapy for CHB also support our findings. After starting NA therapy, HBV decline usually conforms to a biphasic pattern, that is, a rapid first phase in the initial weeks and a slower second phase thereafter [18]. However, the speed of HBV decline in the first phase was not significantly affected by different NAs or dosages in previous randomized studies for HBeAg-positive CHB [20,21]. During the first 12 weeks of NA therapy, telbivudine (LdT) and ETV demonstrated similar viral kinetics [20], and the first-phase HBV decline was also comparable among the TDF, LdT or LdT plus TDF groups [21]. Thus, even though ETV and TDF have not been directly compared, current evidence suggests similar antiviral clearance rates in the first phase among different NAs. Moreover, in a study of high (600 mg daily) versus standard (100 mg daily) LVD dose, although a trend of faster HBV decline in the second phase was found with high-dose LVD (P=0.06), a significant parameter difference in the first phase remained not detected [22]. The first phase reflects suppression of virus production by infected, but the second phase represents a decrease of the infected cell population, which could be affected by multiple factors, such as antiviral potency, antiviral resistance, and immune responses [22,23].

The clinical efficacy of different NA therapies has been compared in CHB with spontaneous SAE in retrospective studies [6,7]. In a cohort study comparing the 24-week efficacies of TDF and ETV, the rate of patient mortality or liver transplantation was similar (TDF versus ETV: 19% versus 18%), and the 12-week and 24-week virological responses were also not significantly different [24]. In a meta-analysis that compared LVD and ETV in the treatment of CHB with spontaneous SAE, the patient survival rates were not significantly different [13,14]. Moreover, the 4-week HBV viral suppression was not significantly different between ETV and LVD [15,16]. However, even though most studies do not show a difference in potency in terms of virus suppression during SAE, the results of retrospective studies are discrepant [13,14]. This prospective study confirms previous findings showing that the ultra-short virological response could not predict clinical outcomes, and the short-term virological response was not significantly different between ETV and LVD. Other prognostic factors may contribute to the differences in outcome. Thus, in order to further improve patient survival, research efforts should investigate methods of effectively controlling other prognostic factors, such as inflammation or immune responses [25–27].

Even having followed the NA therapy stopping rule suggested in the Asian–Pacific practice guidelines [28], most CHB patients who initiated NA therapy due to SAE would suffer from clinical hepatitis relapse after NA discontinuation [10,29]. Unfortunately, among hepatitis relapsers, as high as 18–50% of patients might experience hepatic decompensation again [7,30–32]. Furthermore, some patients could die of liver failure [10]. It remains controversial as to whether a longer duration of consolidation for CHB patients with SAE would reduce the hepatitis relapse rate, and a conservative approach is to treat CHB with NA until HBsAg loss occurs [8]. In addition, the low drug resistance rate in this study, even in LVD users, was compatible with the findings in previous studies for CHB with SAE, for example <5% in 1 year [7]. However, the drug resistance rate on extended LVD treatment could be more than 20% in 4 years [31,32]. Although the efficacy of LVD and ETV was similar in this study, LVD still cannot be recommended as a long-term treatment for CHB patients with SAE due to the concern of drug resistance [33].

Several limitations should be acknowledged in this study. First, the small sample size of this clinical trial limited the statistical power of the analysis and thus it was not possible to infer a definitive conclusion regarding the differences in survival between patients receiving either LVD or ETV therapy. However, this study is the first to report valuable information on the ultra-short virological dynamics after initiating LVD or ETV, which may provide the basis for further investigations aimed at improving patient survival. Second, another clinically preferred newer-generation NA, TDF, was not investigated in this study. Although the 12-week virological responses were not significantly different between TDF and ETV in a retrospective study [24], further studies are needed to confirm the ultra-short virological dynamics after using TDF. Third, the data of this study were limited to 180 days, so the long-term efficacy and safety of NA therapy cannot be directly inferred based on our findings. Lastly, although our data showed that NA therapy could rapidly inhibit HBV replication, some patients still died of hepatic failure. Additional treatment to help improve the efficacy of NA therapy should be further developed.

In conclusion, CHB with spontaneous SAE responded similarly to NA treatment using either LVD or ETV, with both drugs inducing a rapid decline of HBV viral load. Besides early use of NA therapy, additional methods should be investigated to further improve patient survival.

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Disclosure statement

The authors declare no competing interests.

Additional files

Additional file 1: A table displaying the baseline characteristics of all study subjects can be found at https://www.intmedpress.com/uploads/documents/4081_Lee_Addfile1.pdf

Additional file 2: A table displaying the baseline characteristics of study subjects with HBV DNA >6 log IU/ml can be found at https://www.intmedpress.com/uploads/documents/4081_Lee_Addfile2.pdf

Additional file 3: A table displaying the measured outcomes of all study subjects can be found at https://www.intmedpress.com/uploads/documents/4081_Lee_Addfile3.pdf

Additional file 4: A table displaying the measured outcomes of study subjects in the LVD and ETV groups can be found at https://www.intmedpress.com/uploads/documents/4081_Lee_Addfile4.pdf

Additional file 5: A table displaying the univariate analysis in Cox proportional hazards model for risk of mortality/liver transplantation and a table displaying the univariate analysis in logistic regression model for undetectable HBV DNA at year 1 can be found at https://www.intmedpress.com/uploads/documents/4081_Lee_Addfile5.pdf

Additional file 6: A table displaying the measured outcomes of study subjects with HBV DNA >6 log IU/ml and a figure illustrating the dynamic changes of ALT in the LVD and ETV groups can be found at https://www.intmedpress.com/uploads/documents/4081_Lee_Addfile6.pdf

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