A comparison of telbivudine and entecavir for chronic hepatitis B in real-world clinical practice

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Received 25 August 2011; returned 2 October 2011; revised 26 October 2011; accepted 30 October 2011

Objectives: To evaluate the efficacy of telbivudine and entecavir in chronic hepatitis B (CHB) patients over a 1 year period.

Methods: Ninety-seven telbivudine-naive and 98 entecavir-naive CHB patients who had been treated for at least 1 year were enrolled. Serial serum hepatitis B virus (HBV) DNA levels were checked at baseline and at weeks 24 and 48 after treatment.

Results: Entecavir and telbivudine groups had similar baseline HBV DNA levels (5.9 ± 1.7 versus 6.0 ± 1.5 log copies/mL, \(P = 0.529\)). The undetectable rate of HBV DNA after 1 year of treatment was significantly higher in the entecavir group than the telbivudine group (94.9% versus 82.0%, \(P = 0.009\)). Resistance developed in 6.7% of the telbivudine-naive patients after 1 year compared with none of the entecavir-naive patients (\(P = 0.009\)). However, there was a significant difference between the telbivudine and entecavir groups in hepatitis B e antigen (HBeAg) seroconversion 24 weeks after treatment (40% versus 12.5%, \(P = 0.007\)). Multiple logistic regression analysis revealed that baseline alanine aminotransferase (ALT) \(> 200\) IU/L (\(P = 0.008\)) was independently associated with HBeAg seroconversion. Applying the roadmap concept with ALT \(> 2\times\) upper limit of normal at baseline, telbivudine and entecavir had favourable outcomes in PCR negativity, ALT normalization, HBeAg seroconversion and resistance.

Conclusions: In real-world clinical practice, telbivudine resulted in higher rates of HBeAg seroconversion and drug resistance at week 48 compared with entecavir. A combination with baseline ALT plus 24 week HBV DNA levels led to the lowest rates of resistance in HBeAg-positive telbivudine-naive patients and had the highest probability of HBeAg seroconversion in both entecavir- and telbivudine-naive patients.

Keywords: HBV, roadmap, HBeAg seroconversion

Introduction

Despite the availability of highly effective and safe vaccines for more than 20 years, hepatitis B virus (HBV) infection remains the most common worldwide cause of death from liver disease. Approximately 25% of patients with HBV will eventually die of liver failure and hepatocellular carcinoma (HCC) if left untreated. In the REVEAL study, the risk of developing cirrhosis and HCC was directly proportional to serum HBV DNA levels.1 Hence, an effective and prolonged suppression of HBV DNA, which reduces the risk of cirrhosis and HCC, is the primary treatment target.

The roadmap concept was established by Keeffe et al.2 in 2007. Early monitoring of virological responses to therapy in chronic hepatitis B (CHB) treated with oral nucleos(t)ide analogues (NAs) is essential to identify primary treatment failure at week 12 and suboptimal responses at week 24 in order to modify the management accordingly. The GLOBE trial established the superiority of telbivudine over lamivudine in hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients after 1 year and 2 years of therapy.3,4 Notably, telbivudine has a higher rate of HBeAg seroconversion than other current oral anti-viral therapy.5 Although the resistance rate at 2 years for telbivudine is 11%, application of a roadmap concept may reduce this rate.2 Further analysis of the GLOBE trial identified baseline characteristics (so-called super-responders) associated with favourable outcomes after 2 years of telbivudine treatment: (i) HBeAg-positive patients with baseline HBV DNA <9 log copies/mL,
alanine aminotransferase (ALT) >2 times the upper limit of normal (ULN) and undetectable HBV DNA at week 24 and telbivudine resistance of 1.8% at 2 years; and (ii) HBeAg-negative patients with baseline HBV DNA <7 log copies/mL and undetectable serum HBV DNA at week 24 and telbivudine resistance of 2.3% at 2 years.6

Entecavir has been shown to be highly effective at suppressing HBV DNA replication to undetectable levels and normalizing ALT.7 Of note is the very low resistance rate (1.2%) observed in NA-naive HBeAg-negative patients treated with entecavir for up to 5 years. To date, no research has directly compared telbivudine and entecavir for CHB treatment for 1 year. Hence, we designed this cohort study to assess their efficacy and to verify the outcomes by applying the roadmap concept in NA-naive CHB patients.

**Patients and methods**

From June 2008 to October 2010, 98 consecutive treatment-naive CHB patients were treated orally with 600 mg of telbivudine daily at the Chang Gung Memorial Hospital, Taoyuan General Hospital, and Kaohsiung Medical Center for at least 48 weeks (telbivudine group). During this period, 358 treatment-naive CHB patients were treated with 0.5 mg of entecavir daily for at least 48 weeks at the same institution. Of these 358 patients, 99 were randomly selected as the control group (entecavir group). The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. Written informed consent was obtained from each patient.

Patients were followed-up every 3 months for clinical assessments including liver biochemical tests, α-fetoprotein level and serological hepatitis B markers (including HBeAg and antibody to HBeAg). In addition, serum creatine phosphokinase levels were monitored at baseline and weeks 24 and 48. Baseline HBV DNA levels were assessed at baseline and week 24 and week 48 after telbivudine or entecavir treatment. Viral mutational analysis was determined using nested PCR and direct sequencing, as described previously,8 at the time of virological breakthrough.

**Results**

A total of 195 patients were enrolled in this study (97 in the telbivudine group and 98 in the entecavir group). The mean age was older in the telbivudine than the entecavir group (54.3 versus 48.5 years, P=0.003) (Table 1). However, patients in the entecavir group were more often HBeAg positive (P=0.019) and had higher ALT levels (P=0.059) compared with the telbivudine group. The two groups were similar in terms of serum HBV DNA levels (5.9 ± 1.7 versus 6.0 ± 1.5 log copies/mL, P=0.529).

**Efficacy of telbivudine and entecavir at weeks 24 and 48 after treatment**

ALT normalization, HBeAg seroconversion, undetectable HBV DNA and resistance rates between the telbivudine and entecavir groups are shown in Figure 1. After adjusting for age, sex, baseline HBeAg status, baseline ALT and HBV DNA level, there were significant differences between the groups in ALT normalization (80.4% versus 62.5%, P=0.002) and HBeAg seroconversion (40% (10/25) versus 12.5% (5/40), P=0.007) at week 24. At week 48, the proportion of patients in whom HBV DNA levels were undetectable was significantly greater in the entecavir group than in the telbivudine group (94.9% versus 82.0%, P=0.009). Resistance developed in 6.7% of telbivudine-naive patients, compared with none of the entecavir-naive patients (P=0.009). No patient in either group had hepatitis B surface antigen (HBsAg) loss.

**Predictive factors for HBeAg seroconversion at week 24 in telbivudine-naive patients**

Ten (40%) telbivudine-treated patients developed HBeAg seroconversion at week 24. Only baseline ALT >200 IU/L (OR 15.17; 95% CI 2.03–113.35; P=0.008) was independently associated with HBeAg seroconversion.

**Discussion**

In patients with HBeAg-positive CHB, HBeAg seroconversion has been established as a key surrogate marker of treatment response and is associated with improved clinical outcomes. Hence, current treatment guidelines agree that NAs can be stopped after continuing therapy for an additional 6–12 months after HBeAg loss or seroconversion with undetectable HBV DNA for HBeAg-positive patients, except for cirrhosis patients.3 In the present study, telbivudine treatment achieved higher HBeAg seroconversion rates of up to 40% and 47.4% at weeks 24 and 48, respectively, compared with entecavir

<table>
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<th>Table 1. Baseline characteristics of the study population</th>
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<tr>
<td><strong>Telbivudine</strong></td>
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<tr>
<td>Age (years), mean ± SD</td>
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<td>Sex (male:female)</td>
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<td>ALT (IU/L)</td>
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<td>median (range)</td>
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<td>ALT &gt;2×ULN, n (%)</td>
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<td>ALT &gt;5×ULN, n (%)</td>
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<td>Total bilirubin (mg/dL), mean ± SD</td>
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<td>HBeAg-positive, n (%)</td>
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<td>Liver cirrhosis, n (%)</td>
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<td>HCC, n (%)</td>
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<td>HBV DNA (log copies/mL), mean ± SD</td>
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Of note, the HBeAg seroconversion rate in the current study was superior to that in the GLOBE trial. Compared with the GLOBE study, our HBeAg-positive patients had a higher median baseline ALT level (213.6 versus 146.4 IU/L), proportion of ALT >2× ULN (72% versus 64%) and ALT >5× ULN (36% versus 16%). Further analysis indicated that there was an

Figure 1. Comparison of efficacy results between telbivudine and entecavir at weeks 24 and 48. LdT, telbivudine; ETV, entecavir.

Figure 2. Comparison of efficacy results between telbivudine and entecavir with the recommended baseline of ALT and roadmap concept. LdT, telbivudine; ETV, entecavir.
increasing trend of HBeAg seroconversion rate based on higher baseline ALT levels in both the telbivudine and entecavir groups. In the telbivudine group, 14%, 44% and 67% of patients with baseline ALT levels $<2\times$, $2–5\times$ and $>5\times$ ULN, respectively, achieved HBeAg seroconversion after 1 year of treatment. In the entecavir group, 27%, 20% and 32% of patients achieved HBeAg seroconversion with baseline ALT levels $<2\times$, $2–5\times$ and $>5\times$ ULN, respectively. Multivariate analysis showed that ALT level ($>200$ IU/L) was an independent predictive factor for HBeAg seroconversion. According to a prior study by Liaw, $^{10}$ ALT levels $>5\times$ ULN reflect a more robust immune clearance of HBV and induce a greater chance of HBV-DNA clearance and HBeAg seroconversion, both in the natural course and in drug therapy, which may explain the better outcomes in HBeAg seroconversion.

To check for efficacy and compliance, as well as to modify therapy for those with suboptimal responses, on-treatment responses are as critical as pre-treatment profiles. In the present study we combined the baseline characteristics of ALT $>2\times$ ULN and on-treatment responses at week 24 and found that entecavir and telbivudine had similar efficacies in PCR negativity and ALT normalization (Figure 2). Regarding virological resistance, there were no variants resistant to entecavir by week 48. Therefore, our study confirms entecavir has a high genetic resistance barrier in real-world clinical practice. In contrast, six patients developed virological resistance at week 48 after telbivudine treatment, of whom, five had M204I mutations and one had a M204I/L80V double mutation, which is consistent with previous findings. $^{10}$ In our study, five patients received add-on adefovir treatment, resulting in an undetectable HBV DNA level after a median follow-up period of 13 (range 5–18) months. Only one patient was switched to an entecavir regimen. After 18 months the serum HBV DNA had declined to a low level, but was still detectable (2.8 log copies/mL). Owing to the small number of patients developing telbivudine resistance in our study, no predictors of resistance could be identified. Both entecavir and telbivudine had excellent safety and tolerability in this study, with both having different features and advantages in CHB treatment. Entecavir had a better profile compared with telbivudine in terms of resistance; however, telbivudine showed significantly higher rates of HBeAg seroconversion. A combination with baseline ALT plus 24 week HBV DNA levels led to the lowest rates of resistance in HBeAg-positive telbivudine-naive patients and had the highest probability of HBeAg seroconversion in both entecavir- and telbivudine-naive patients. Hence, using a proper strategy taking pre-treatment characteristics and on-treatment responses into consideration, antiviral agents with different features and advantages may provide physicians with a wider choice of options with which to treat CHB.

Acknowledgements

We thank Jasmine Lien, PhD, for her editorial assistance in the development of this manuscript, and Vincent Yeh for his excellent technical assistance.

Funding

This study was supported by research grant CMRPG-8A0061G from Chang Gung Memorial Hospital. Technical assistance from Vincent Yeh was supported by Medical Science Liaison, Novartis (Taiwan) Co., Ltd. The funding bodies played no role in the study.

Transparency declarations

The authors have no conflicts of interest to declare. Language editing services were provided by ATS Medical Editing and Review Solutions.

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