A comparison of efficacy and safety of 2-year telbivudine and entecavir treatment in patients with chronic hepatitis B: a match–control study

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Abstract

There are limited data comparing the clinical outcomes between telbivudine and entecavir. We consecutively enrolled 115 telbivudine-naive and 115 entecavir-naive chronic hepatitis B patients, who were matched for age, sex, hepatitis B e antigen (HBeAg) status and cirrhosis, and treated for at least 2 years or less than 2 years but had developed resistance. Except for the rate of HBeAg seroconversion, which was similar, patients in the entecavir group had better clinical outcomes than those in the telbivudine group for alanine aminotransferase normalization (85.2% vs 78.4%, p <0.048), undetectable HBV DNA (96.5% vs 74.8%, p <0.001), and viral resistance (0.9% vs 21.7%, p <0.001) after 2 years of treatment, After applying roadmap or super-responders concepts, entecavir still had better outcomes than telbivudine in undetectable HBV DNA and viral resistance. The cumulative incidence of hepatocellular carcinoma development was similar between telbivudine-naive and entecavir-naive patients (p 0.565). In renal function analysis, there were significantly more patients with estimated glomerular filtration rate (eGFR) category improvement in both the telbivudine and entecavir groups at year 1 (p 0.006 and p 0.047, respectively). The rate of virological improvement was significantly higher with entecavir than with telbivudine after 2 years of treatment, whether applying the concepts of roadmap or super-responders. The incidence of hepatocellular carcinoma was similar between telbivudine and entecavir. Both telbivudine and entecavir were associated with eGFR improvement, especially in patients with renal insufficiency.

Keywords: Chronic hepatitis B, entecavir, renal function, roadmap, telbivudine
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Introduction

Although highly effective vaccines to prevent hepatitis B virus (HBV) infection have been available since 1982, there are still more than 350 million chronic carriers, 75% of whom reside in the Asia Pacific region [1]. These patients are at risk of developing hepatic decompensation, cirrhosis and hepatocellular carcinoma (HCC). With an expanded range of treatment options and a substantial improvement in the understanding of predictors of response to therapy, the management of patients with chronic hepatitis B (CHB) continues to evolve. Currently, there are five oral nucleos(t)ide analogues approved for the treatment of CHB [2], including three nucleoside analogues (lamivudine, telbivudine and entecavir) and two nucleotide analogues (adefovir and tenofovir). Each of these agents is effective in rapid and profound suppression of viral replication, facilitating hepatitis B e antigen (HBeAg) seroconversion, achieving alanine aminotransferase (ALT) normalization, and improving liver fibrosis. However, there are limited direct head-to-head trials comparing the different antiviral agents.

The registration trials of telbivudine and entecavir were compared with lamivudine, and tenofovir was compared with adefovir [3–5]. Although our previous study compared the efficacy of telbivudine and entecavir, there are many limitations including the small size of patient groups, only 1 year of comparison, and a heterogeneous baseline [6].

The concept of roadmap, proposed by Keeffe *et al.* [7], uses the 24-week virological response to minimize long-term resistance. From the GLOBE trial, although the resistance rate at 2 years for telbivudine is 11%, application of a roadmap concept may reduce this rate. Further analysis from the GLOBE trial identified optimal baseline characteristics plus undetectable HBV DNA at week 24 after treatment (so-called super-responders) is associated with favourable outcomes after 2 years of telbivudine treatment. These were: (i) HBeAg-positive patients with baseline HBV DNA $<10^9$ copies/mL, ALT $>2 \times$ upper limit of normal (ULN) and undetectable HBV DNA at week 24; (ii) HBeAg-negative patients with baseline HBV DNA $<10^7$ copies/mL and undetectable serum HBV DNA at week 24 [8]. However, in real-world clinical practice, there are limited data to support this concept.

With higher numbers of patients now being treated for CHB, possible adverse events have gained more attention. One area of concern is renal function. Adefovir and tenofovir are both acyclic nucleotide analogues structurally, which have been shown to be nephrotoxic [9–12]. However, it should be noted that recent retrospective analyses from clinical studies demonstrated that long-term telbivudine treatment is associated with steady improvement in renal function, including in patients with pre-existing renal disease and those receiving tenofovir, although the potential mechanisms are unclear [13]. There is no published study indicating this finding and it is not known whether long-term treatment with entecavir affects renal function.

The present study aimed to compare the efficacy and safety of telbivudine and entecavir in patients who received therapy for 2 years.

Patients and Methods

Study design and patients

This was a retrospective single-centre match–control study. Between April 2007 and October 2012, a total of 115 CHB patients naive-treated with 600 mg telbivudine daily at the Chang Gung Memorial Hospital, Kaohsiung Medical centre for at least 2 years or less than 2 years and who had developed virological resistance were enrolled in this study. The sample population comprised 88 (77%) men and 27 (23%) women, with mean age ($\pm$ SD) 52.9 $\pm$ 12.4 years. A total of 28 (24%) patients were positive for HBeAg and 57 (50%) had cirrhosis. To compare the efficacy and safety of telbivudine and entecavir, 115 hepatitis B surface antigen-positive patients treated with 0.5 mg entecavir daily for at least 2 years were selected randomly, who matched for age, gender, HBeAg status and cirrhosis. Of these 230 patients, 186 patents eligible for this trial were recruited from our previous study conducted in our centre (telbivudine, $n = 94$; entecavir, $n = 92$, respectively) [6]. The remaining 44 patients who were treated with telbivudine or entecavir between June 2007 and October 2010 and fitted the enrolled criteria were added to the study.

The therapeutic strategy for CHB patients was based on the criteria approved by the Bureau of National Health Insurance of Taiwan in 2008. Briefly, the criteria for treatment of CHB patients are as follows: (i) seropositivity for HBV surface antigen pulse decompensated liver disease; (ii) elevated ALT levels $\geq 5 \times$ ULN (≥ 200 IU/L) for HBeAg-positive patients; (iii) elevated ALT levels between $2 \times$ and $5 \times$ ULN ($80 <$ ALT <200 IU/L) with HBV DNA levels $>10^5$ copies/mL for HBeAg-positive patients without clinical evidence of cirrhosis; (iv) elevated ALT levels $\geq 2 \times$ ULN (≥ 80 IU/L) with HBV DNA levels $>10^4$ copies/mL for HBeAg-negative patients without clinical evidence of cirrhosis; and (v) HBV DNA levels $>10^4$ copies/mL for patients with clinical evidence of cirrhosis. Clinical cirrhosis was defined by one of the followings: (i) ultrasonographic evidence of small liver with splenomegaly and/or (ii) presence of oesophageal or cardiac varices. Patients were excluded if they had any evidence of autoimmune hepatitis or markers of hepatitis C, hepatitis D and human immunodeficiency virus, or patients received chemotherapy or immunosuppressant agents, and significant intake of alcohol (20 g/day for women; 30 g/day for men).

Patients were followed up every 3 months or less for clinical assessment, including conventional liver biochemical tests, α-fetoprotein level, and serological hepatitis B markers (including HBeAg and antibody to HBeAg). Serial HBV DNA levels were assessed at baseline, and every 6 months after treatment. Virological breakthrough was defined as either an increase of serum HBV DNA of at least 1 log copies/mL from the nadir for patients with detectable viral load, or serum HBV DNA >100 copies/mL for patients with undetectable viral load during treatment [14]. The viral mutational analysis was determined using nested PCR and direct sequencing, as described previously [15], at the time of virological breakthrough. In addition, ultrasonography was performed for the surveillance of HCC every 3–6 months. If tumour was suspected, dynamic computed tomography or magnetic resonance imaging or liver biopsy studies were performed for confirmation. The diagnosis of HCC was based on the