Efficacy of telbivudine on hepatitis B viral status and liver function in patients with hepatitis B virus-related hepatocellular carcinoma

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Efficacy of telbivudine on hepatitis B viral status and liver function in patients with hepatitis B virus-related hepatocellular carcinoma

Directed by Professor Sang Hoon Ahn

The Master's Thesis
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ABSTRACT

Efficacy of telbivudine on hepatitis B viral status and liver function in patients with hepatitis B virus-related hepatocellular carcinoma

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Background: Antiviral therapy with nucleos(t)ide analogues has been shown to be effective in improving liver function in patients with chronic hepatitis B (CHB). However, antiviral efficacy and safety of telbivudine therapy, one of the nucleoside analogues for CHB has not been evaluated in hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC).

Methods: A total of 223 CHB patients consecutively treated with 600 mg/day telbivudine for at least 6 months, 80 had HCC (HCC group; A) whilst 143 did not have HCC (non-HCC group; B). During telbivudine treatment, biochemical, virological and serological parameters were regularly monitored.

Results: There was no significant difference in baseline characteristics between two groups. The median duration of telbivudine treatment was 16.1 months. At Month 21, a median change in serum HBV DNA from baseline was similar between the groups (A *vs* B: -3.5 *vs* -4.0 $\log_{10}$ IU/ml, P = 0.671). The

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cumulative complete virologic response (serum HBV DNA < 12 IU/ml) was also comparable (A *vs* B: 57.5% *vs* 65.7%, *P* = 0.318). ALT normalization was 63% in the HCC group and 81% in the non-HCC group. HBeAg seroconversion was 5.7% in the HCC group and 4.4% in the non-HCC group. The cumulative rate of viral breakthrough was higher in the non-HCC group, but it could not reach to significant difference (17.5% vs 29.3%, P = 0.055). There was no hepatitis flare in both group, representing telbivudine was effective to prevent HBV reactivation during anti-HCC treatment. Telbivudine treatment improved liver function showing an increase in serum albumin level (*P* <0.001) and decrease in Child-Pugh scores (*P* <0.001). No serious side effects were found in all patients.

Conclusion: Telbivudine had comparable antiviral efficacy and safety both in patients with HCC and non-HCC. During telbivudine treatment, there appears to be no hepatitis flare due to HBV reactivation from anti-HCC treatment and liver function of patients has been improved.

Key Words : chronic hepatitis B, hepatocellular carcinoma, telbivudine

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Efficacy of telbivudine on hepatitis B viral status and liver function in patients with hepatitis B virus-related hepatocellular carcinoma

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I. INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world[1] and is characterized by grave prognosis with poor survival[2]. HCC is commonly detected at an advanced stage, and only 10-30% of HCC cases are eligible for curative surgical resection at the time of tumor diagnosis[3, 4]. Although diverse therapeutic approaches, such as transarterial chemoembolization (TACE), hepatic artery infusion chemotherapy (HAIC), concurrent chemoradiation therapy (CCRT), and sorafenib have been attempted in advanced HCC patients, overall response rates have been unsatisfactory and the median survival time is less than 1 year from the time of initial diagnosis[5].

In particular, 70-80% of HCC patients in Asia have hepatitis B virus (HBV) infection, and a large number of patients with HCC are simultaneously diagnosed with HBV infection[2, 6]. Previous studies have demonstrated that

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prolonged HBV suppression using antiviral therapy in patients with HBV-related HCC is equally important as treating the tumor, because the maintenance of underlying liver function can assist in deciding HCC treatment strategies and improve overall survival[1, 7, 8].

Several nucleos(t)ide analogues (NAs) have been developed over the past decade, and used to treat chronic hepatitis B (CHB)[9, 10]. In addition to lamivudine, there are currently four oral NAs available for treatment of CHB, including adefovir dipivoxil, entecavir, telbivudine, clevudine and tenofovir, which have all shown greater antiviral activity compared with placebo or lamivudine in patients with CHB[11-15].

Based on the results of the GLOBE trial, telbivudine (ß-L-2'-deoxythymidine), as a synthetic nucleoside analogue and bioavailable L-nucleoside with specific anti-HBV activity *in vitro*, has become a new option for clinicians to treat the patients with CHB[9, 16]. The GLOBE trial showed that telbivudine has more potent anti-viral activity and less viral resistance compared with lamivudine[12].

However, the efficacy of antiviral therapy on HBV status and underlying liver function in patients with HBV-related HCC is still unclear. Thus, it has been investigated whether telbivudine treatment for patients with HBV-related HCC could also induce biochemical, serological and virological improvements as much as in CHB patients without HCC.

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II. MATERIALS AND METHODS

1. Patients

All consecutive patients with chronic hepatitis B (CHB) in Severance Hospital (Seoul, South Korea) who started on telbivudine 600 mg once daily between March 2010 and September 2011 were enrolled in this study.

Inclusion criteria were serum HBsAg present ≥6 months, age ≥16 years, previously treatment-naïve, with subsequent treatment period of at least 6 months of telbivudine. Telbivudine was commenced when serum HBV DNA was over 10,000 copies/mL for hepatitis B e antigen (HBeAg)-positive patients, over 1,000 copies/mL for hepatitis B e antigen (HBeAg)-negative patients and when either ALT level was >2 x upper limit of normal or liver biopsy showed significant fibrosis/cirrhosis. The exclusion criteria were 1) younger than 16 years, 2) previous antiviral treatment for CHB, 3) survival time of less than 6 months after enrollment, 4) insufficient data, 5) poor compliance with the antiviral drug regime, 6) coexistence of other malignancies or serious medical illness, 7) co-infection with hepatitis C or D virus or human immunodeficiency virus, 8) transfer to other hospital or loss of follow-up. A total of 223 patients were fulfilled with the above criteria and followed up for analysis.

2. Study design

From March 2010 to September 2011, all consecutive patients with CHB who

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have taken oral telbivudine 600 mg once daily were analyzed. All patients underwent baseline examinations, including serum HBV DNA, detection of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and anti-HBe, liver function tests (ALT, AST, total bilirubin, albumin and total protein), creatinine levels, prothrombin time and complete blood counts (white cell counts, hemoglobin and platelet counts). Liver function tests, HBeAg, anti-HBe and HBV DNA were monitored every 3-6 months thereafter.

Virological response was defined as undetectable serum HBV DNA (<12 IU/ml) by polymerase chain reaction (PCR) at any time point during telbivudine therapy. Virologic breakthrough (VB) was defined as an increase in serum HBV DNA of >1 $\log_{10}$ IU/ml from the nadir during telbivudine therapy. Biochemical response (BR) was defined as normalization of serum ALT level from abnormal baseline levels; a threshold of 40 IU/l was used as the upper limit of normal (ULN) range. Biochemical breakthrough (BB) was defined as an increase in serum ALT level above the ULN after achieving ALT normalization. Serological response was defined as HBeAg loss or HBeAg seroconversion in HBeAg positive patients. HBeAg seroconversion was defined as the loss of HBeAg with the development of anti-HBe on at least two consecutive follow-ups. Genotypic resistance was defined as the appearance of viral populations bearing amino acid substitutions in the reverse transcriptase region of the HBV genome that conferred resistance to antiviral drugs in patients with VB. Liver cirrhosis was defined as follows: (1) liver cirrhosis confirmed by biopsy, (2) either

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current or past evidence of cirrhosis-related complications (for example, ascites, varices or hepatic encephalopathy) or (3) a platelet count <100,000/mm^3 with ultrasonographic findings suggestive of cirrhosis, including a blunted or nodular liver edge accompanied by splenomegaly (>12 cm).

3. Diagnosis of HCC and staging system

Diagnosis of HCC was based on pathologic confirmation or typical appearance of HCC on either two dynamic imaging examinations (computed tomography and magnetic resonance imaging) or one dynamic imaging technique with elevated serum alpha-fetoprotein (AFP; >400 ng/mL). HCC was staged using the TNM system, based on modified Union for International Cancer Control (UICC) classifications, – which was adopted from the Liver Cancer Study Group of Japan.

4. Laboratory assay

Serum HBV DNA levels were quantified with a real-time PCR assay on a COBAS TaqMan 48 analyzer (Roche Molecular Systems, Branchburg, NJ, USA; the lower detection limit was 12 IU/ml). HBV serological tests for HBsAg, HBeAg, and anti-HBe were conducted with enzyme-linked immunoassays (Dade Behring, Marburg, Germany). Biochemical data including levels of ALT, AST, total bilirubin, albumin, creatinine, platelet and prothrombin time were measured using a sequential multiple auto-analyzer

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(Hitachi Ltd., Tokyo, Japan). Genotypic resistance to telbivudine was analyzed using restriction fragment mass polymorphism (RFMP), as previously described[17-19]. Analytical sensitivity in detecting telbivudine-resistant strains was estimated to be 300 copies/ml.

5. Statistical analysis

Continuous variables were expressed as means ± standard deviations (SDs). Serum HBV DNA concentration was expressed on a logarithmic scale. Baseline characteristics of the HCC and non-HCC groups were compared by Student's *t*-test for continuous variables and a chi-square test (or Fisher's exact test) for categorical variables. The Kaplan-Meier method was used to determine the cumulative incidences of ALT normalization, HBeAg seroconversion, viral breakthrough and HBV DNA non-detectable rates by PCR. Results were considered to be statistically significant when $P < 0.05$. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

III. RESULTS

1. Patient characteristics

A total of 223 CHB patients who have been treated with telbivudine were enrolled, of these, 80 patients had concurrent HCC (HCC group) and 143 did not have HCC (non-HCC group). The baseline characteristics of the two groups are summarized in Table 1. The mean duration of telbivudine therapy was 15.7

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months in the HCC group and 16.4 months in the non-HCC group ($P = 0.144$). Compared with the HCC group, the non-HCC group had significantly higher AST and ALT levels ($P < 0.001$ in both). Serum albumin level was also higher in the non-HCC group ($P < 0.001$). The other parameters such as age, sex, liver cirrhosis rate, platelet, bilirubin, prothrombin time, HBeAg positivity rate, serum HBV DNA and splenomegaly rate were not significantly different between two groups.

Table 1. Baseline characteristics of patients

Characteristic	Total (n=223)	HCC group (n=80)	Non-HCC group (n=143)	*P* value
Age (year)	53.3±11.0	57.9±10.4	50.7±10.6	0.075
Sex (male/female)	136/87	55/25	81/62	0.185
Liver cirrhosis (%)	123(55.2)	51(63.8)	72(50.3)	0.054
AST (IU/L)	67.8±60.3	48.0±33.3	79.0±68.8	<0.001
ALT (IU/L)	69.9±74.6	38.7±23.7	87.4±86.8	<0.001
Platelet ($x10^3/mm^3$)	147.0±57.9	134.8±60.6	154.8±55.0	0.146
Total bilirubin (mg/dl)	1.0±0.9	0.9±0.7	1.0±1.0	0.324
Albumin (g/dl)	3.9±0.5	3.6±0.6	4.0±0.5	<0.001
Prothrombin time (INR)	1.0±0.1	1.0±0.1	1.0±0.1	0.448
HBeAg positivity (%)	102(45.7)	35(43.8)	67(46.9)	0.655
HBV DNA (log_{10} IU/ml)	6.0±1.2	5.7±1.1	6.2±1.3	0.264
Splenomegaly (%)	101(45.3)	43(53.8)	58(40.6)	0.058
Duration of telbivudine (months)	16.1±4.6	15.7±4.2	16.4±4.8	0.144

The baseline tumor characteristics, initial anti-HCC treatment modality and survival of the HCC group are listed in Table 2. Among HCC patients, 9 patients were dead during telbivudine therapy. The causes of deaths were disease progression for 5 patients, septic shock due to pneumonia for 2 patients and esophageal variceal bleeding for 2 patients. There was no anti-HCC

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treatment-related death.

Table 2. Baseline tumor and clinical characteristics in patients with HCC

Tumor characteristics	Value (number)
Tumor size (<2/2-5/5-10/≥10cm)	18/40/18/4
Tumor number (1/2/3-4/≥5)	37/17/15/11
Tumor type (well-defined/ill-defined)	53/27
Portal vein invasion (yes/no)	19/61
Modified UICC stage (I/II/III/IVa/IVb)	25/31/14/9/1
Initial treatment (surgery/RFA/TACE/chemotherapy/ supportive care)	24/3/44/8/1
Number of survivors (yes/no)	71/9
Mean follow-up duration from diagnosis (months)	15.7±4.2
Child-Pugh score (A/B/C)	40/10/1

2. Effect of telbivudine on hepatitis B viral status

When compared clinical outcomes between the two groups during 21 months of telbivudine therapy, it was found that the cumulative rates of ALT normalization in the HCC and non-HCC group were 93.5% (29/31) and 92.4% (86/93), respectively (Fig. 1A); the cumulative rates of HBeAg seroconversion were 5.7% (2/35) and 4.4% (3/67), respectively (Fig. 1B); the cumulative rates of viral breakthrough were higher in the non-HCC group (29.4% *vs* 17.5%) but it could not reach to statistical significance ($P = 0.055$) (Fig. 1C, Table 3); the cumulative rates of virological response were 57.5% (46/80) and 65.7% (94/143), respectively (Fig. 1D).

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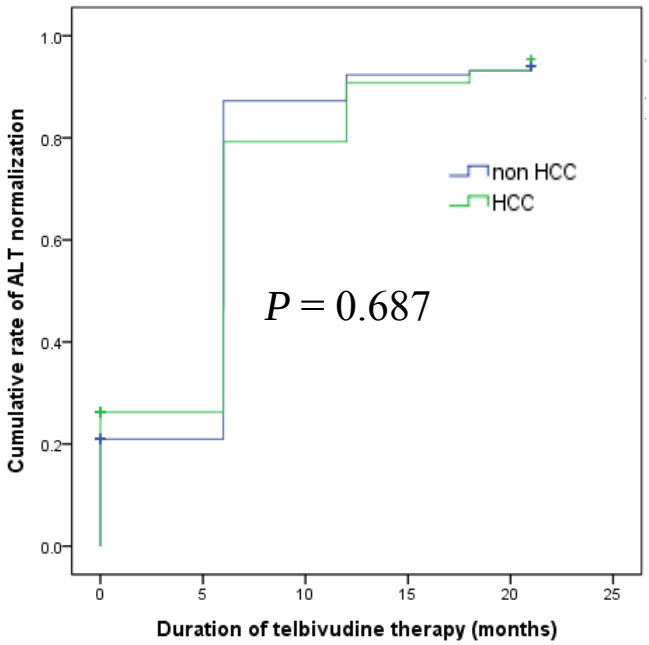
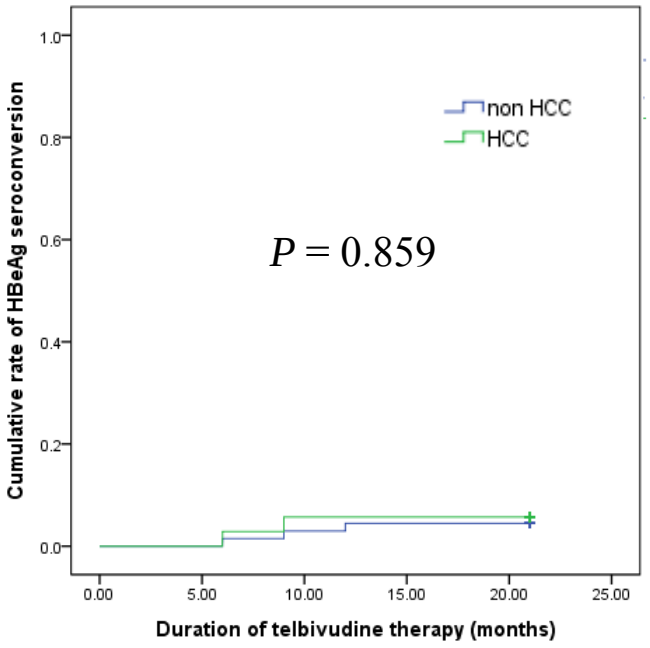
A.

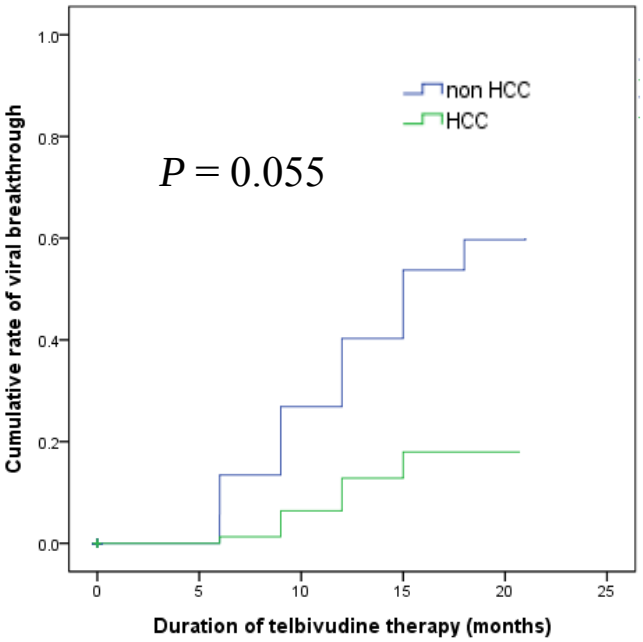

Cumulative rate of ALT normalization
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
Duration of telbivudine therapy (months)
non HCC
HCC
P = 0.687

B.

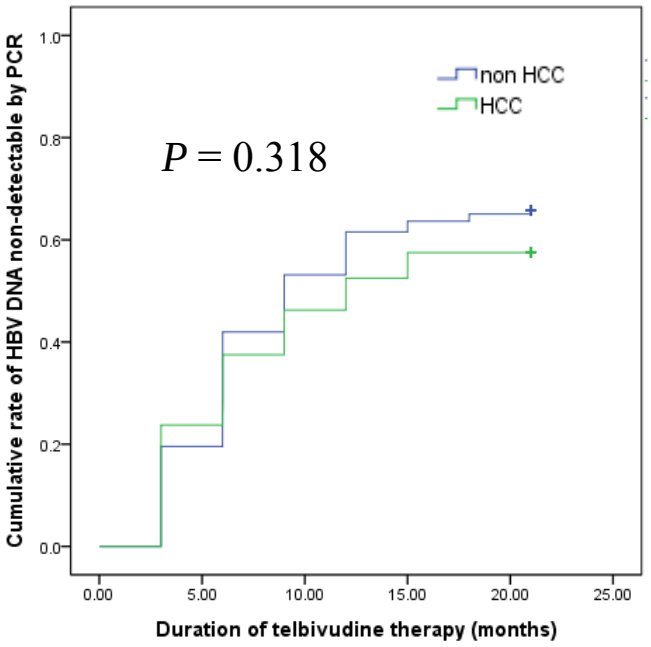

Cumulative rate of HBeAg seroconversion
1.0
0.8
0.6
0.4
0.2
0.0
0.00
5.00
10.00
15.00
20.00
25.00
Duration of telbivudine therapy (months)
non HCC
HCC
P = 0.859

``

C.


non HCC
HCC
P = 0.055
Cumulative rate of viral breakthrough
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
Duration of telbivudine therapy (months)

D.


non HCC
HCC
P = 0.318
Cumulative rate of HBV DNA non-detectable by PCR
1.0
0.8
0.6
0.4
0.2
0.0
0.00
5.00
10.00
15.00
20.00
25.00
Duration of telbivudine therapy (months)

``

Fig. 1. Effects of telbivudine on hepatitis B viral status in the HCC group and non-HCC groups. (A) Cumulative rates of ALT normalization during 21 months of telbivudine therapy. The cumulative rates were 93.5% (29/31) in the HCC group and 92.4% (86/93) in the non-HCC group. (B) Cumulative rates of HBeAg seroconversion during 21 months of telbivudine therapy. The cumulative rates were 5.7% (2/35) in the HCC group and 4.4% (3/67) in the non-HCC group. (C) Cumulative rates of viral breakthrough during 21 months of telbivudine therapy. The cumulative rates were 17.5% (14/80) in the HCC group and 29.4% (42/143) in the non-HCC group. (D) Cumulative rates of virological response were 57.5% (46/80) in the HCC group and 65.7% (94/143) in the non-HCC group.

The mean decline of serum HBV DNA from baseline was significant in the both groups. At Month 21, a mean change of serum HBV DNA was -3.5 $\log_{10}$ IU/ml in the HCC group and -4.0 $\log_{10}$ IU/ml in the non-HCC group ($P = 0.671$) (Table 3). The viral breakthrough rates were 17.5% in the HCC group and 29.4% in the non-HCC group without significant difference. The rate of viral breakthrough in combination with genotypic resistance was similar between the groups (12.5% in HCC *vs* 14.7% in non-HCC, $p = 0.651$). There was no hepatitis flare up during anti-HCC treatment in HCC group during the follow-up (Table 3).

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Table 3. Virological response on telbivudine therapy

Variables	HCC group (n=80)	Non-HCC group (n=143)	*P* value
Median log_{10} HBV DNA at baseline	5.7±1.1	6.2±1.3	0.264
Median change in HBV DNA, log_{10} IU/ml			
From baseline to month 3	-3.3±1.4	-3.4±1.5	0.527
From baseline to month 6	-3.7±1.3	-3.8±1.5	0.182
From baseline to month 9	-3.9±1.4	-4.0±1.7	0.106
From baseline to month 12	-3.9±1.7	-4.2±1.8	0.930
From baseline to month 15	-3.9±1.7	-4.2±1.8	0.930
From baseline to month 18	-4.9±1.6	-4.8±2.1	0.190
From baseline to month 21	-3.5±2.0	-4.0±1.8	0.671
HBV DNA < 12 IU/ml			
Month 3, n/N (%)	19/80 (23.8%)	28/143 (19.6%)	0.464
Month 6, n/N (%)	29/80 (36.3%)	56/143 (39.2%)	0.668
Month 9, n/N (%)	31/74 (41.9%)	56/129 (43.4%)	0.833
Month 12, n/N (%)	31/67 (46.3%)	57/117 (48.7%)	0.749
Month 15, n/N (%)	29/56 (51.8%)	47/103 (45.6%)	0.458
Month 18, n/N (%)	12/25 (48.0%)	26/61 (42.6%)	0.648
Month 21, n/N (%)	4/10 (40.0%)	12/37 (32.4%)	0.654
Antiviral resistance at Month 21			
VB	14/80 (17.5%)	42/143 (29.4%)	0.055
VB + GR	10/80 (12.5%)	21/143 (14.7%)	0.651
Hepatitis flare	0	0	0.999

Variables are expressed as mean ± SD or n (%)
GR, genotypic resistance; VB, virologic breakthrough
Hepatitis flare was defined as the elevation of ALT level to more than 10 times of the upper normal limit.

3. **Effect of telbivudine on underlying liver function**

The effect of telbivudine therapy on underlying liver function was evaluated in the HCC and non-HCC groups by measuring Child-Pugh scores and several laboratory parameters before and after telbivudine treatment (Table 4). The ALT level showed significant change from 69.9±74.6 IU/L at baseline to 35.4±40.7 after 12 months of telbivudine therapy ($P < 0.05$). AST level (67.8±60.3 *vs.* 45.7±56.5), albumin levels (3.9±0.5 *vs.* 4.1±0.5) and Child-Pugh scores

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(5.6±1.2 *vs*. 5.3±0.9) also showed significant change ($P < 0.05$).

Table 4. Changes in liver function during telbivudine therapy in all patients (n=223)

Variables	Baseline	12 months	P value
AST (IU/L)	67.8±60.3	45.7±56.5	0.001
ALT (IU/L)	69.9±74.6	35.4±40.7	<0.001
Albumin (g/dl)	3.9±0.5	4.1±0.5	<0.001
Child-Pugh score	5.6±1.2	5.3±0.9	<0.001

IV. DISCUSSION

There have been increasing evidence that telbivudine treatment can induce biochemical, virological and serological improvements in CHB patients without HCC[9, 20, 21]. However, the antiviral efficacy of telbivudine therapy on viral suppression and change of underlying liver function in patients with HBV-related HCC has not been reported. This study demonstrated the benefits of telbivudine therapy for patients with HBV-related HCC.

During 24 months of telbivudine therapy in GLOBE study, the rates of ALT normalization were 69.5% in patients with HBeAg-positive CHB and 77.8% in patients with HBeAg-negative CHB[12]. Similar rates of ALT normalization, 63% and 81% in the HCC group and non-HCC group, respectively were shown in this study. No significant difference in HBeAg positivity was also shown between the two groups (HCC *vs*. non-HCC group, 43.8% *vs*. 46.9%).

Telbivudine treatment resulted in significant improvements in underlying liver function in this study, as shown by an increase in serum albumin level and

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decreased AST, ALT and Child-Pugh scores. These results suggested that telbivudine has a benefit on improving liver function.

In this study, the rate of liver cirrhosis was slightly higher in HCC group (63.8%) than that (50.3%) of non-HCC group without statistical difference. However, the increase of the cumulative rates of ALT normalization and serum HBV DNA reduction were similarly found in each group. This result suggests compatible efficacy of telbivudine between non-cirrhotic and cirrhotic patients.

The prognosis of decompensated cirrhosis is dismal, and 3-5% of patients with compensated HBV cirrhosis has been reported to develop hepatic decompensation[3, 5, 7]. Similar to non-cirrhotic patients with CHB, HBV-host interaction may continue in cirrhotic patients, and the annual incidence of hepatitis flares in HBV cirrhosis has been estimated at 10-20%[3, 24-26]. Although the majority of hepatitis flares was self-limited, approximately 10-20% were complicated by hepatic decompensation[25]. Moreover, treatment strategies for HBV-related HCC, including surgical resection, radiation therapy and systemic chemotherapy have resulted in HBV reactivation and exacerbation of hepatitis[4, 22, 23, 25]. Therefore, antiviral treatment to control viral replication and thus to improve underlying liver function in managing patients with HBV-related HCC, may be as important as treating the tumor themselves. In this study, telbivudine treatment led to improvement of liver function and absence of hepatitis flare through successful viral suppression. Therefore, this study might advocate the necessity of antiviral therapy in HBV-related HCC patients.

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Many studies have proven that antiviral treatment in patients with HCC resulted in successful treatment of the tumors[3]. Likewise, telbivudine can restore HBV-associated viral and biochemical deterioration in patients with HBV-related HCC by improving underlying liver function and making the more aggressive treatment of HCC possible.

V. CONCLUSION

In conclusion, this study demonstrated that virological, serological and biochemical responses of telbivudine therapy were similar between CHB patients with and without HCC. Telbivudine treatment improved underlying liver function and prevented hepatitis flare due to HBV reactivation. These findings suggest that telbivudine treatment in patients with HBV-related HCC may be beneficial for active treatment of HCC.

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REFERENCES

1. Ahn SH, Chan HL, Chen PJ, Cheng J, Goenka MK, Hou J, et al. Chronic hepatitis B: whom to treat and for how long? Propositions, challenges, and future directions. Hepatology international 2010;4:386-95.
2. Ahn SH, Yuen L, Han KH, Littlejohn M, Chang HY, Damerow H, et al. Molecular and clinical characteristics of hepatitis B virus in Korea. Journal of medical virology 2010;82:1126-34.
3. Tziomalos K. Effect of antiviral treatment on the risk of hepatocellular carcinoma in patients with chronic hepatitis B. World journal of hepatology 2010;2:91-3.
4. Kim JH, Park JW, Koh DW, Lee WJ, Kim CM. Efficacy of lamivudine on hepatitis B viral status and liver function in patients with hepatitis B virus-related hepatocellular carcinoma. Liver Int 2009;29:203-7.
5. Song HU, Hwang SG. [Prevention of hepatocellular carcinoma]. The Korean journal of gastroenterology = Taehan Sohwagi Hakhoe chi 2007;49:201-8.
6. Ahn SH, Park YN, Park JY, Chang HY, Lee JM, Shin JE, et al. Long-term clinical and histological outcomes in patients with spontaneous hepatitis B surface antigen seroclearance. Journal of hepatology 2005;42:188-94.
7. Cheng SQ, Wu MC, Chen H, Shen F, Yang JH, Cong WM, et al. [Anti-viral therapy using lamivudine and thymosin is helpful to prevent recurrence in hepatocellular carcinoma with coexisting active hepatitis B]. Zhonghua zhong liu za zhi [Chinese journal of oncology] 2005;27:114-6.
8. Hann HW. Active antiviral therapy for chronic hepatitis B and hepatocellular carcinoma. Minerva gastroenterologica e dietologica 2008;54:19-30.
9. Buti MA. [Telbivudine in the treatment of the chronic B hepatitis]. Gastroenterol Hepatol 2008;31:258-63.
10. Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. Hepatology 2009;49:S185-95.
11. Hann HW. Telbivudine: an effective anti-HBV drug for chronic hepatitis B patients with early on-treatment responses. Expert opinion on pharmacotherapy 2010;11:2243-9.
12. Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, et al. 2-Year GLOBE trial results: telbivudine Is superior to lamivudine in patients with chronic hepatitis B. Gastroenterology 2009;136:486-95.
13. Matthews SJ. Telbivudine for the management of chronic hepatitis

``

B virus infection. Clin Ther 2007;29:2635-53.
14. McKeage K, Keam SJ. Telbivudine: a review of its use in compensated chronic hepatitis B. Drugs 2010;70:1857-83.
15. Yurdaydin C, Akarca US. Treatment of chronic hepatitis B with telbivudine: wise hepatologists needed in hepatitis B endemic countries where treatment options are limited. Liver Int 2011;31:589-91.
16. Gane EJ, Wang Y, Liaw YF, Hou J, Thongsawat S, Wan M, et al. Efficacy and safety of prolonged 3-year telbivudine treatment in patients with chronic hepatitis B. Liver Int 2011;31:676-84.
17. Kim HS, Han KH, Ahn SH, Kim EO, Chang HY, Moon MS, et al. Evaluation of methods for monitoring drug resistance in chronic hepatitis B patients during lamivudine therapy based on mass spectrometry and reverse hybridization. Antiviral therapy 2005;10:441-9.
18. Lee JM, Ahn SH, Kim HS, Park H, Chang HY, Kim do Y, et al. Quantitative hepatitis B surface antigen and hepatitis B e antigen titers in prediction of treatment response to entecavir. Hepatology (Baltimore, Md) 2011;53:1486-93.
19. Han KH, Hong SP, Choi SH, Shin SK, Cho SW, Ahn SH, et al. Comparison of multiplex restriction fragment mass polymorphism and sequencing analyses for detecting entecavir resistance in chronic hepatitis B. Antiviral therapy 2011;16:77-87.
20. Telbivudine: rhabdomyolysis and neuropathy. Prescrire Int 2010;19:171.
21. Ahn SH, Kweon YO, Paik SW, Sohn JH, Lee KS, Kim DJ, et al. Telbivudine in combination with adefovir versus adefovir monotherapy in HBeAg-positive, lamivudine-resistant chronic hepatitis B. Hepatology international 2011.
22. Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. Hepatology (Baltimore, Md) 2006;43:209-20.
23. Kim JH, Park JW, Kim TH, Koh DW, Lee WJ, Kim CM. Hepatitis B virus reactivation after three-dimensional conformal radiotherapy in patients with hepatitis B virus-related hepatocellular carcinoma. International journal of radiation oncology, biology, physics 2007;69:813-9.
24. Shen YC, Hsu C, Chen LT, Cheng CC, Hu FC, Cheng AL. Adjuvant interferon therapy after curative therapy for hepatocellular carcinoma (HCC): a meta-regression approach. J Hepatol 2010;52:889-94.
25. Mahmood S, Niiyama G, Kamei A, Izumi A, Nakata K, Ikeda H, et al.

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Influence of viral load and genotype in the progression of Hepatitis B-associated liver cirrhosis to hepatocellular carcinoma. Liver Int 2005;25:220-5.
26. Romano PR, McCallus DE, Pachuk CJ. RNA interference-mediated prevention and therapy for hepatocellular carcinoma. Oncogene 2006;25:3857-65.

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ABSTRACT (IN KOREAN)

B형 간염 바이러스에 의한 간암 환자에서 바이러스 억제 및 간기능 향상에 대한 텔비부딘의 효능 평가

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배경: 뉴클레오사이드 / 뉴클레오티드 유사체와 같은 항바이러스제 치료는 만성 B형 간염 환자의 간기능에 개선에 도움이 되는 것으로 알려져 있다. 그러나 현재까지 B형 간염 바이러스에 의한 간암 환자에서 텔비부딘의 항바이러스 효과와 안전성은 밝혀져 있지 않다.

방법: 적어도 6개월 이상 하루 600 mg 텔비부딘을 복용한 총 223명의 만성 간염 환자들을 대상으로 하였다. 만성 B형 간염 바이러스에 의한 간암 환자는 80명 (간암 환자군, A), 만성 B형 간염만 있는 환자는 143명 (비간암 환자군, B)이 연구에 참여하였다. 이들을 대상으로 텔비부딘 치료 기간 동안의 생화학적, 바이러스학적, 혈청학적 지표들을 정기적으로 관찰하였다.

결과: 처음 두 그룹간의 생화학적, 바이러스학적, 혈청학적 지표들은 차이가 없었다. 텔비부딘을 복용한 중간값은 16.1 개월이었다. 21개월동안 추적 관찰한 결과 양 군의 혈청 HBV DNA 감소량은 A군과 B군 각각에서 중간값 -3.5 $\log_{10}$ IU/ml 와

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-4.0 $\log_{10}$ IU/ml (P = 0.671) 이었다. 완전 바이러스 반응인 혈청 HBV DNA 가 12 IU/ml 이하로 감소된 누적율은 양 군에서 각각 57.5%와 65.7%로 두 군간의 유의한 차이는 없었다. (P = 0.318) 혈청 HBV DNA 감소율도 양 군에서 각각 57.5%, 65.7% 였고 통계적으로 유의한 차이는 없었다. ALT 정상화 비율은 간암 환자와 비간암 환자군에서 각각 63%, 81% 였다. HBeAg 혈청 전환률은 간암 환자와 비간암 환자 군에서 각각 5.7%, 4.4% 였다. 단, 텔비부딘 항생제 내성을 갖는 비율은 간암 환자와 비간암 환자군에서 각각 17.5%, 29.3%로 비간암 환자군에서 높게 나타났으나, 통계적으로 유의한 차이는 없었다. (P = 0.055). 치료 기간 중 양 군에서 돌발성 간염은 없었으며 이는 텔비부딘이 간암을 치료할 때 B형 간염의 재활성을 막는데 효과가 있다는 것을 나타낸다고 할 수 있다. 또한 텔비부딘 치료 후 알부민 값의 상승 (P <0.001)과 Child-Pugh score의 감소 (P <0.001)를 확인할 수 있었고 이로 미루어 텔비부딘 치료는 간기능의 향상을 가져옴을 알 수 있었다. 모든 환자에서 텔비부딘의 심각한 부작용은 관찰되지 않았다.

결론: 본 연구를 통해 간암 환자와 비간암 환자에서 텔비부딘의 효능에 차이가 없음을 알 수 있었다. 텔비부딘 치료를 하는 동안 간암 치료를 받는 환자에서 B형 간염의 재활성을 통한 돌발성 간염은 나타나지 않았고 간기능의 향상되는 것을 알 수 있었다.

핵심되는 말 : B형 간염 바이러스, B형 간염, 간암, 텔비부딘

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