CLINICAL, BIOCHEMICAL AND VIROLOGICAL RESPONSES TO ENTECAVIR IN PATIENTS WITH HBV - RELATED CIRRHOSIS

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Summary

Background: Limited data is available from Vietnam on the outcome and efficacy of entecavir in hepatitis B virus (HBV) - related cirrhosis. This study aims to investigate clinical, biochemical and virological responses in patients with HBV - related cirrhosis treated with entecavir. *Subjects and methods:* 93 patients with HBV - related cirrhosis were examined and treated at Danang Hospital from Dec 2016 to June 2019. Of these, 59 patients with compensated cirrhosis and 34 patients with decompensated cirrhosis. Drugs: Entecavir (Baraclude^{R}) was given a dose of 0.5mg and 1mg per day for compensated and decompensated cirrhosis, respectively, 2 hours after breakfast, monitor for 12 months. *Results:* Entecavir treatment of 12 months resulted in a marked improvement in common clinical symptoms including anorexia, fatigue, jaundice ($p < 0.001$) and edema ($p < 0.01$). Significantly decreased the Child - Pugh score (5.75 ± 1.06 compared to 6.43 ± 1.63 points). Normalized rates of AST and ALT were 67.74% and 78.49%, respectively, of which the compensated cirrhotic group had a higher rate than the decompensated group (AST: 76.27% vs 52.94%; ALT: 88.14% vs 61.76%). The rate of achieving HBV DNA < 20IU/mL increased with time of treatment after 6 months was 34.4% and after 12 months reached 76.3%. There is no significant effect of entecavir on renal function and metabolism of serum calcium and lactate. *Conclusion:* Entecavir is an effective and safe treatment option for patients with HBV - related cirrhosis, especially exerts a better effect on patients with compensated cirrhosis that may improve the prognosis of cirrhotic patients.

Key words: Entecavir, HBV, cirrhosis.

BACKGROUND

Chronic hepatitis B virus (HBV) infection is a burden in healthcare globally and is associated with a high risk of serious complications including cirrhosis and hepatocellular carcinoma[6]. Vietnam is in the high endemic area with HBV infection at the rate of 10 - 20% population[9] and the rate of cirrhosis due to HBV accounts for about 50% of cirrhosis cases[2]. Once cirrhosis has progressed, the prognosis without prompt treatment is poor, with a 5 year survival rate of approximately 85% for compensated cirrhosis and less than 15% for decompensated cirrhosis[3].

It was previously thought that in cirrhosis the virus no longer replicates. However, the advancement of molecular biology has been demonstrated that even at the cirrhosis stage, replication of HBV exists and this is a factor related to the progression of the disease[15]. More importantly, recent studies have shown that antiviral therapy in patients with HBV - related cirrhosis can improve liver function, reduce complications and prolong patient survival[12,14]. However, in Vietnam, there are not many studies evaluating the efficacy and safety of entecavir in cirrhotic patients. Therefore, we carry out this study to investigate the clinical, biochemical and viral response in patients with HBV - related cirrhosis treated with entecavir.

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SUBJECTS AND METHODS

Subjects: Patients > 18 years old and ≤ 75 years old, attending the Department of Gastroenterology or Gastrointestinal Clinic, Danang Hospital, from September 2016 to July 2019. 93 patients were meeting the following criteria:

* Criteria for selecting patients:

- Viral criteria: Patients with HBsAg(+) > 6 months and/or anti - HBs IgG(+) and serum HBV DNA load ≥ 2000IU/mL.

- Criteria for diagnosis of cirrhosis: In the absence of liver biopsy, there must be at least 2 of the following 4 criteria[13]:

+ Liver ultrasound: based on signs such as rough liver structure or nodular lesions, irregular margins, dilated portal vein, large spleen, groin... or esophageal varices and/or stomach during endoscopy.
+ Platelet reduction < 100 x 109/L.
+ INR > 1.3 or blood albumin decreased < 35g/L.

Patients were divided into 2 groups: compensated and decompensated cirrhosis.

Exclusion criteria: patients had previous treatment with tenofovir, adefovir, had anti - HCV(+), anti - HIV(+), alcoholic hepatitis, alcoholism or cancer.

Methods: Research design: prospective. Study variables: AST, ALT, bilirubin, albumin, creatinine, lactate, AFP, HBeAg, anti - HBe, HBV - DNA, INR, platelet, Child - Pugh score.

Quantitative HBV - DNA: real - time PCR technique, on COBAS AmpliPrep - COBAS TaqMan 48 machine of Roche (USA). Performed at the Department of Microbiology, Danang Hospital. The detection threshold is 20UI/ml (100 copies/ml).

- Drugs: Entecavir of BMS company (BaracludeR), 0.5mg/day for compensated cirrhosis and 1 mg/day for decompensated cirrhosis.

- Data processing: By EXEL and SPSS 22.0, the difference is statistically significant when $p < 0.05$.

RESULTS

93 patients with HBV - related cirrhosis were enrolled in this study. Of these, 55 (59,1%) male and 38 (40,9%) female; 59 patients had compensated cirrhosis and 34 patients had decompensated cirrhosis.

Patients characteristics

Significant improvements in clinical symptoms with time compared to baseline were anorexia (from 92.5% to

Table 1. Patients characteristics

Characteristics	Compensated cirrhosis (n = 59)	Decompensated cirrhosis (n = 34)	Total (n = 93)	P * & **
Age (yrs)	52.49 ± 11.61	51.59 ± 7.56	52.16 ± 10.28	> 0.05
Male (n,%)	38 (64.4)	17 (50.0)	55 (59.1)	< 0.05
AST (U/L)	87.19 ± 18.51	88.36 ± 35.80	87.62 ± 26.00	> 0.05
ALT (U/L)	67.35 ± 23.54	60.39 ± 28.03	64.80 ± 25.35	> 0.05
Bilirubin TP (µmol/l)	17.40 (13.3 – 23.7)	38.05 (25.26 – 50.75)	21.90 (15.15 - 31.25)	**< 0.001**
Albumin (g/l)	36.90 ± 4.01	27.47 ± 5.18	33.46 ± 6.37	**< 0.001**
Child-Pugh	5.49 ± 0.60	8.06 ± 1.58	6.43 ± 1.63	**< 0.001**
HBV - DNA (x 10^3IU/mL)	24.95 (15.4 – 32.05)	16.20 (9.44 - 93.76)	20.57 (13.44 - 16.63)	> 0.05
INR	1.17 ± 0.10	1.43 ± 0.22	1.27 0.20	**< 0.001**
Platelet	99.07 ± 29.61	64.79 ± 24.37	86.54 ± 32.27	**< 0.001**

There was no significant difference between the 2 groups in terms of age, sex, AST activity, ALT and HBV DNA. Total bilirubin, INR, and Child - Pugh scores were significantly lower in the compensated cirrhosis group ($p < 0.001$). In contrast, the serum albumin and platelet concentrations were significantly higher in the compensated cirrhosis group ($p < 0.001$).

Treatment response

Clinical response

Table 2. Clinical response

Timespoint / Symptoms/signs	Baseline (n = 93) (a)	After 6 M (n = 93) (b)	After 12 M (n = 93) (c)	P	
				(a)&(b)	(a)&(c)
Anorexia (n,%)	86 (92.5)	9 (9.7)	0 (0)	**< 0.001**	-
Fatigue (n,%)	90 (96.8)	33 (35.5)	13 (14.0)	**< 0.001**	**< 0.001**
Insomnia (n,%)	16 (17.2)	0 (0)	0 (0)	-	-
Abdominal pain (n,%)	36 (38.7)	4 (4.3)	2 (2.2)	**< 0.001**	**< 0.001**
Spider nodules (n,%)	70 (75.3)	67 (72.0)	67 (72.0)	> 0.05	> 0.05
Jaundice (n,%)	40 (43.0)	19 (20.4)	12 (12.9)	**< 0.01**	**< 0.001**
Edema (n,%)	13 (14.0)	3 (3.2)	2 (2.2)	**< 0.05**	**< 0.01**
Ascites (n,%)	11 (11.8)	9 (9.7)	7 (7.5)	> 0.05	> 0.05
Collateral circulation (n,%)	30 (32.3)	29 (31.2)	28 (30.1)	> 0.05	> 0.05
Hepatosplenomegaly (n,%)	12 (12.9)	12 (12.9)	12 (12.9)	> 0.05	> 0.05

9.7% after 6 months), fatigue (from 96.8% to 14% after 1 year), abdominal pain (from 38.7% to 2.2% after 12 months), jaundice (from 43% to 12.9% after 12 months), edema (from 14% to 2.2% after 12 months).

Other symptoms such as spider nodules, ascites, collateral circulation and hepatosplenomegaly were almost unchanged or the changes were not statistically significant (p > 0.05).

Table 3. Response of Child-Pugh scores

Child Pugh (n, %)	M0	M6	M12
Child A	62 (66.7)	73 (78.5)	76 (81.7)
Child B	24 (25.8)	20 (21.5)	17 (18.3)
Child C	7 (7.5)	0	0
Mean	6.43 ± 1.63	5.86 ± 1.15	5.75 ± 1.06
p (to baseline 6.43 ± 1.63)	**< 0.01**	**< 0.001**	

After 6 months of treatment there were no longer Child C patients. At the end of 12 months of treatment, an additional 14 patients with Child A and a decrease of 7 patients in Child B group. The Child - Pugh score decreased significantly over time of treatment, after 6 months (p < 0.01) and after 12 months (p < 0.001).

After 12 months there was a slight increase in serum

Biochemical response

Table 4. Normalizing AST and ALT

Timespoints	Patients followed	Compensated (n = 59)	Decompensated (n = 34)	Total (n = 93)	p
Normalizing AST (n, %)					
6 months	93	42 (71.19)	13 (38.24)	55 (59.14)	< 0.001
12 months	93	45 (76.27)	18 (52.94)	63 (67.74)	< 0.001
Normalizing ALT (n, %)					
6 months	93	49 (83.05)	16 (47.06)	65 (69.89)	< 0.001
12 months	93	52 (88.14)	21 (61.76)	73 (78.49)	< 0.01

The rate of normalizing AST and ALT activities increased gradually with time of treatment. However, this rate was significantly higher in the compensated cirrhosis group than in the decompensated cirrhosis group at all evaluation points (p < 0.001).

Virological response

Table 5. HBV - DNA

Timespoints	Patients followed	Compensated cirrhosis	Decompensated cirrhosis	Total	p
HBV - DNA medians					
Baseline[a]	93	24,955 (15,400 - 320,500)	16,200 (9,442 - 93,758)	20,565 (13,441 - 166,364)	> 0.05
6 months[b]	93	91 (0 - 259)	136 (17.25 - 1242.2)	100 (0 - 446.5)	> 0.05
12 months[c]	93	0 (0 - 0)	0 (0 - 27)	0 (0 - 0)	> 0.05
p	(a) & (b)	**< 0.001**			
	(c) & (a)				
Rate of HBV - DNA below the threshold					
Sau 6 M	93	24 (40.7)	8 (23.5)	32 (34.4)	> 0.05
Sau 12 M	93	47 (79.7)	24 (70.59)	71 (76.3)	< 0.001
p		**< 0.001**			

After 12 months HBV - DNA load decreased significantly in both cirrhosis groups (p < 0.001) and no difference at follow - up times between the 2 groups (p > 0.05). Similarly, the rate of reaching HBV - DNA below the threshold also increased gradually with treatment time (p < 0.001) and there was no difference between the 2 groups (p > 0.05).

Influences of entecavir treatment on renal function, calcium and lactate

Table 6. Influences of entecavir treatment on renal function, calcium and lactate

Markers	Baseline	After 12 M	Changing	p
Creatinin (µmol/L)	67.49 ± 13.45	68.40 ± 14.09	0.91 ± 9.59	> 0.05
GRF (mL/min./1.73m^2)	105.84 ± 22.53	102.72 ± 21.77	-3.12 ± 17.76	> 0.05
Lactate (mmol/L)	2.59 ± 0.52	2.69 ± 0.57	0.10 ± 0.58	> 0.05
Calcium (mmol/L)	1.16 ± 0.05	1.15 ± 0.05	-0.01 ± 0.05	> 0.05

creatinine levels (mean increase of 0.91 ± 9.59µmol/L) and a decrease in glomerular filtration (mean decrease in GRF: -3.12 ± 17.76mL/min/1.73m^2). Similarly, there was a slight increase in lactate concentration and decrease in calcium concentration (p > 0.05).

DISCUSSIONS

HBV is the most common cause in patients with chronic hepatitis. Among them, 10 - 20% lead to cirrhosis[4]. Treatment that sustainably inhibits HBV replication is seen as the cornerstone of treatment for HBV - related cirrhosis[5]. Recent research has shown that antiviral therapy can improve clinical consequences and reduce the incidence of HCC in patients with HBV - related cirrhosis[6,13]. Entecavir has been recommended as one of the preferred drugs for the treatment of chronic hepatitis B[4] and recent studies have shown that entecavir is relatively safe and effective in patients with HBV - related cirrhosis[1,5,6,8].

Results of our study showed that 12 month entecavir treatment showed a marked improvement in common clinical symptoms such as anorexia (from 92.5% to 0%), fatigue (96.8% to 14%), edema (from 14% to 2.2%), right side pain (from 38.7% to 2.2%), jaundice (from 43% to 12.9%)... However, there was no improvement in the rates of signs such as spider nodules, collateral circulation, hepatosplenomegaly (p > 0.05). This result is similar to that of Tran V. Huy, Nguyen T. Huyen Thuong (2016)[2] evaluated the efficacy of tenofovir also in patients with cirrhosis of HBV. The results showed that the most obvious improvement was anorexia (from 77.5% to 7.7%); edema (from 42.5% to 7.5%). This difference is statistically significant (p < 0.05). Symptoms of hepatomegaly and spider nodules were almost unchanged after treatment.

The Child - Pugh score is considered as a useful scoring system for assessing liver function and clinical prognosis in cirrhotic patients[14]. Our research shows that after 6 months there are no longer any Child C patients (initially 7 patients with Child C). At the end of 12 months of treatment an increase of 14 additional Child A patients (from 62 to 76 patients) and a decrease of 7 patients with

Child B (from initial 24 to 17 patients). Child - Pugh score changed significantly according to treatment time compared with baseline, after 6 months (5.86 ± 1.15 vs 6.43 ± 1.63 points, $p < 0.01$) and after 12 months (5.75 ± 1.06 vs 6.43 ± 1.63 points, $p < 0.001$). According to a study by Tran V. Huy, Nguyen T. Huyen Thuong (2016)[2] there was a significant improvement in Child - Pugh scores after antiviral treatment in HBV - induced cirrhosis. There were 7 patients in the study group from Child C to Child B, 6 patients from Child B to Child A. After 9 months, the mean Child - Pugh index remained 5.94 ± 0.22. This improvement is statistically significant ($p < 0.05$). According to Gai et al (2017)[5], the Child - Pugh score decreased significantly in the group with compensated cirrhosis with time of treatment and for the group with decompensated cirrhosis a significant decrease from only 48 weeks of treatment compared to baseline. According to this author, Child - Pugh scores improved or stabilized in all patients with compensated cirrhosis at the end of 96 weeks of treatment. However, in the decompensated cirrhosis group, 11 patients had a deteriorating Child - Pugh score at the end of treatment. This evidence suggest that long-term treatment with entecavir may improve liver function, slow the progression of cirrhosis and reduce complications related to cirrhosis.

The rate of normalizing the activity of AST and ALT increased gradually over time of treatment, at the end of 12 months of treatment were 67.74% and 78.49%, respectively. However, this rate was significantly higher in the compensated cirrhosis group than in the decompensated cirrhosis group at all evaluation points ($p < 0.001$). Our results are similar to some studies at home and abroad[1,5,8]. According to Tran V. Huy and Nguyen P. Bao Quan (2016), the study on the efficacy of tenofovir in patients with compensated HBV cirrhosis showed that the normalization rates of ASL and ALT at 12 months of treatment were 91.7 respectively. % and 87.5%[1].

The persistence of HBV replication in cirrhotic patients is considered to be an important factor in the progression of the disease. Therefore, treatment to sustainably inhibit HBV replication will prevent or reduce the progression of the disease to decompensated cirrhosis[14]. After 12 months of entecavir treatment, there was a statistically significant reduction in HBV - DNA load in both groups over treatment time ($p < 0.001$) and no difference at follow - up times between 2 groups ($p > 0.05$). Similarly, the rate of achieving HBV - DNA below the threshold also increased gradually with treatment time ($p < 0.001$), but after 12 months, the rate of reaching HBV - DNA below the threshold was higher in the compensated cirrhosis group than in the decompensated cirrhosis group (79, 7% vs 70.59%, $p < 0.001$). Our results are similar to Tran V. Huy et al (2016) on the treatment of tenofovir in HBV - compensated cirrhosis patients, after 12 months, the rate of HBV - DNA below the threshold reached 81.3% of cases[1]. According to Gai et al (2017), the entecavir study in HBV- induced cirrhosis showed that in the compensated cirrhosis group there was a rapid decrease in HBV - DNA load after only 24 weeks of treatment. Meanwhile, for the decompensated cirrhosis group this decrease was only significant after 96 weeks of treatment and the rate of reaching HBV - DNA below the threshold in the compensated cirrhosis group was also higher than the decompensated group, 78.2 respectively. % and 47.1% ($p < 0.01$)[5].

Safety of entecavir in cirrhotic patients: Our study showed a slight increase in creatinine from baseline (mean increase of 0.91 ± 9.59µmol/L) at the same time a decrease in glomerular filtration rate (GRF: -3.12 ± 17.76mL/min/1.73m^2), ($p > 0.05$). This result is similar to some research results in Vietnam and abroad[2,10]. According to Tran V. Huy et al (2016), after 9 months of tenofovir treatment, there was no change in serum creatinine concentration[2], according to Park et al (2017), there was no adverse effect of entecavir. and tenofovir on renal function after 2 years of treatment[10]. Despite this, several other studies have noted a low percentage of patients with increased serum creatinine levels during prolonged entecavir (36 months with 1.11% of cases) and tenofovir (45 months with 5, 45% of cases).

This evidence suggest that long - term NA therapy requires periodic monitoring of renal function, especially in patients with impaired glomerular filtration, combined diabetes and using diuretics[10]. In addition, there was a slight decrease in serum calcium concentration, but this change was not statistically significant ($p > 0.05$). Similarly, changes in serum lactate concentrations were not significant in our study. However, some studies have found a low proportion of patients with lactic acidosis, especially in patients with severe hepatic impairment. According to the study of Lange et al (2009), when treating entecavir in cirrhotic patients, there were 5/16 cases of lactic aci-

dosis and all of these cases had MELD score ≥ 20 points. In contrast, in patients with MELD < 18 points, there was no case of hyperlactatemia[7]. This evidence suggest that lactic acidosis should be closely monitored in patients with impaired liver function and MELD score ≥ 20 points on treatment with oral antivirals.

CONCLUSIONS

Treatment with entecavir 12 months on 93 patients with HBV - related cirrhosis significantly improved the common clinical symptoms including anorexia, fatigue, jaundice ($p < 0.001$) and edema ($p < 0.01$), significantly decrease in Child - Pugh score (5.75 ± 1.06 compared to 6.43 ± 1.63 points). The rate of normalized enzyme AST and ALT was 67.74% and 78.49% respectively, in which the rate of compensated cirrhosis group is higher than decompensated cirrhosis. The rate of achieving HBV DNA load < 20IU/mL was 76.3%, of which the compensated cirrhosis group is higher than the decompensated cirrhosis group (79.7% vs 70.59%, $p < 0.001$).

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