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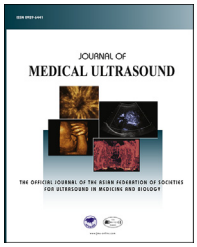

ORIGINAL ARTICLE

Long-term Nucleos(t)ides Analogues for Chronic Hepatitis B Improve Liver and Spleen Size: A Noninvasive Sonographic Study

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KEYWORDS
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Abstract *Background:* Histological improvement and regression of liver fibrosis after long-term use of nucleos(t)ides analogues (NUCs) have been documented. The aim of the present investigation was to evaluate the usefulness of traditional sonography to detect hepatic and splenic changes during NUC therapy in chronic hepatitis B (CHB) patients.
Methods: A total of 181 CHB patients receiving NUC treatment were enrolled in this study. The study population was divided into three groups: 72 cirrhotic, 58 noncirrhotic CHB, and 51 non-replicative hepatitis B virus carriers. All patients had blood chemistries taken and sonography at baseline and during the NUC treatment period. The changes in liver size, liver edge, spleen size, platelet count, and platelet count/spleen diameter (PC/SD) ratio were compared among the three groups of patients.

Abbreviations: AFP, α-fetoprotein; ALT, alanine transaminase; AST, aspartate transaminase; CHB, chronic hepatitis B; Hb, hemoglobin; HBV, hepatitis B virus; INR, international normalized ratio; NUCs, nucleos(t)ides analogues; PC/SD, platelet count/spleen diameter; WBC, white blood cells.

Conflicts of interest: All authors do not have an association that might pose a conflict of interest.

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Results: CHB Patients with and without cirrhosis have improved clinical features during NUC therapy with lower aspartate aminotransferase, alanine aminotransferase, international normalized ratio, hepatitis B virus DNA, and spleen size and higher platelet, liver edge, liver size, and PC/SD ratio compared with the baseline data ($p < 0.05$). The differences in liver edge, liver size, spleen size, and PC/SD ratio are higher in the cirrhosis group than in the noncirrhotic group ($p < 0.001$). A decrease in spleen size exhibited a linear relationship with treatment duration ($R^2 = 0.905$).
Conclusions: Traditional sonography is helpful to monitor changes in liver fibrosis of CHB patients under NUC therapy.
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Introduction

Chronic hepatitis B (CHB) is one of the major causes of liver cirrhosis and hepatocellular carcinoma [1,2]. Antiviral nucleos(t)ides analogue (NUC) therapy is effective in achieving viral suppression, and their long-term use leads to histological improvement and regression of liver fibrosis [3,4]. Liver biopsy is the gold standard of histological diagnosis; however, it has the disadvantage of being invasive [5—9].

Ultrasonography is easily accessible and convenient in daily clinical practice to evaluate liver disease severity. Ultrasonography is routinely performed in clinical follow-up of patients with chronic liver disease for cirrhosis and hepatocellular carcinoma surveillance according to clinical practice guidelines [10,11]. Several studies demonstrated platelet count and splenic size ratio as a reliable predictor of esophageal varices [12,13]. An early study depicted that spleen size was significantly larger in cirrhotics than in noncirrhotics [14]. Recent studies showed spleen diameter and platelet count as a more reliable noninvasive method to detect clinically significant portal hypertension in patients with compensated cirrhosis [15,16].

The aim of the present investigation is to evaluate the usefulness of ultrasonography to detect alterations in disease severity during NUC therapy in CHB patients.

Patients and methods

Ethics statement

The present study was approved by the Institutional Review Board of the Cathay General Hospital (CGH-P102068) under the ethical guidelines of Helsinki Declaration. Informed consent was waived as the data were analyzed anonymously.

Study population

We conducted a retrospective study of 181 consecutive hepatitis B virus (HBV) carriers in Cathay General Hospital Medical Center, which consisted of 72 cirrhotic and 58 noncirrhotic CHB patients undergoing regular NUC therapy to compare with 51 nonreplicative HBV carriers who did not require NUC therapy. All patients were followed up for more than 12 months. All patients with hepatitis other than HBV, malignancy, or other major systemic diseases were excluded. Thirty-five cirrhotic patients had liver histology to confirm the clinical diagnosis of cirrhosis, and the remaining 37 patients had upper endoscopies to confirm the presentation of esophageal varices. All 58 noncirrhotic patients were confirmed by liver histology.

We defined cirrhosis CHB patients as those with ultrasonographic findings of coarse echotexture, uneven hepatic surface, tortuous narrowed hepatic veins, and splenomegaly or with esophageal varices on upper gastrointestinal panendoscopy. Noncirrhotic CHB patients were defined as those with no sign of cirrhosis on ultrasonography with episode(s) of abnormal transaminases ($\geq$1.5$\times$ upper normal limit). Nonreplicative HBV carriers was defined as undetectable HBV DNA ($<$17 IU/mL) and no episode of elevated transaminases ($<$1.5 upper normal limit).

Methods

All patients were examined for their age, sex, blood chemistries, and ultrasonography at baseline and during the NUC treatment period. The blood chemistries were collected every 3 months for serum level of aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, hemoglobin (Hb), white blood cells (WBCs), platelet count, prothrombin time [PT; international normalized ratio (INR)], and α-fetoprotein (AFP). The sonography (iU22; Philips Ultrasound, Bothell, WA, USA) was assessed under overnight fasting status every 6 months by the one physician (SSY) to avoid interobserver variations. We use a C5-1 broadband curved array transducer with a median frequency of mainly 3.5 MHz (range, 3—5 MHz) to examine the liver and spleen. For each measurement, at least three reproducible spectral patterns were made to calculate the spleen diameter, liver edge, and liver size.

The maximal spleen size is measured as longitudinal coronal plan encompassing the splenic hilum [17] (Figure 1). The liver size is measured as the craniocaudal diameter at the midsternal line [18] (Figure 2). Liver edge is measured at the midsternal line and is presented as degree of angle [19,20] (Figure 3).

Statistical analysis

The comparison of demographics and clinical characteristics between cirrhotic, noncirrhotic, and nonreplicative

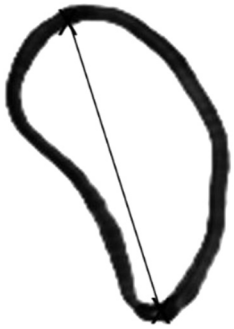

Figure 1 Schematic spleen size is measured as longitudinal coronal plan encompassing splenic hilum.

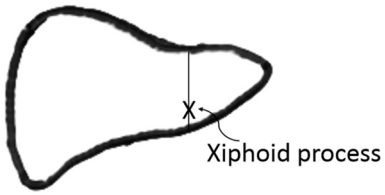

Figure 2 Schematic liver size is measured as craniocaudal diameter of at the midsternal line.

Figure 3 Schematic liver edge is measured at the midsternal line and is presented as degree of angle.

HBV carriers were analyzed by one-way analysis of variance for continuous variables. Dichotomous data were expressed as sample size, and descriptive data were expressed as mean $\pm$ standard deviation. All tests of significance were two-tailed, and a p value of less than 0.05 was considered statistically significant.

We summarized the changes in splenic diameter of cirrhotic patients and used interpolation for computing the average alterations in spleen size during the treatment period. All statistical analyses and graphs were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA), Microsoft Office Excel 2007 (Microsoft, Redmond, WA, USA) and SPSS program for Windows 16.0 (SPSS Inc., Chicago, IL, USA).

Results

The baseline characteristics of three patient groups are summarized in Table 1. There is no difference in age among the three groups ($p > 0.05$). CHB patients with and without cirrhosis have higher AST ($p = 0.002$), ALT ($p < 0.001$), INR ($p = 0.006$), HBV DNA ($p = 0.005$), spleen size ($p < 0.001$) and lower platelet ($p < 0.001$), liver size ($p = 0.002$), and PC/SD ratio ($p < 0.001$) than nonreplicative HBV carriers.

All cirrhotic and noncirrhotic patients developed undetectable HBV DNA levels under NUC therapy. There was no difference in NUCs between the two treatment groups. CHB patients with and without cirrhosis have improved clinical features during NUC therapy with lower AST, ALT, INR, HBV DNA, and spleen size and higher platelet, liver edge, liver size, and PC/SD ratio compared with the baseline data ($p < 0.05$, Table 2).

In addition, differences in liver edge, liver size, spleen size, liver size, and PC/SD ratio are higher in the cirrhosis group than in the noncirrhotic group ($p < 0.001$), whereas change in nonreplicative HBV carrier group is not obvious (Table 3). Figure 4 shows the moving average of spleen size in 5 years of follow-up. At baseline, the average spleen size was 10.26 cm. In the following 30 months, it decreased slightly to 9.61 cm (coefficient of determination, $R^2 = 0.905$). Variation in average spleen size between 31 and 60 months is largely attributed to the limited number of patients undergoing long-term treatment.

Discussion

The clinical assessment of the degree of liver fibrosis is important for the progression to cirrhosis and the decision to start treatment [21]. It is not practical and considered of high risk to repeat invasive procedures such as liver biopsy [22]. A noninvasive and highly reproducible method for assessing liver fibrosis to monitor the staging of liver fibrosis is important clinically to improve patient safety, care quality, and accuracy [8]. Transient elastography has been developed to evaluate the staging liver fibrosis despite some limitations [23,24]. Transient elastography has been reported to assess the regression of HBV related cirrhosis under NUC therapy [25]. However, transient elastography lacks evaluation of other features of cirrhosis such as splenomegaly or the changes in liver angle, which can be detected on ultrasonography.

Splenomegaly and thrombocytopenia were the common complications of portal hypertension and liver cirrhosis [14,26]. In liver cirrhosis, the spleen enlarges as a result of portal hypertension and platelet sequestration [14,26]. In this study, we showed that long-term NUC therapy can increase liver size, decrease spleen size, increase platelet count, and increase the PC/SD ratio. Similar results were reported in chronic hepatitis C virus (HCV)-related cirrhosis with improved portal pressure, platelet counts, and spleen size after sustained viral response of HCV treatment [27].

Our data from cirrhotic patients show increased liver size upon NUC therapy. The increase in liver size is likely to result from liver regeneration and suppression of hepatic injury by NUC therapy. In the present data, those noncirrhotic patients without NUCs also had a lesser degree of increase in liver size and decreased splenic size compared with cirrhotic patients with long-term NUC therapy. However, the mean liver and splenic size of nonreplicative HBV carriers was not significantly changed. The cirrhotic patients initially had much higher splenomegaly prior to NUC therapy compared with noncirrhotic patients. It is not

Table 1 Comparison of demographic and clinical characteristics among three groups of hepatitis B virus carriers at baseline.

	Cirrhosis CHB (n = 72)	Noncirrhosis CHB (n = 58)	Nonreplicative Carrier (n = 51)	p
Age (y)	56.46 ± 11.93	55.14 ± 11.07	51.59 ± 8.91	0.05
Sex				0.01
Male	56 (77.78%)	40 (68.97%)	27 (52.94%)	
Female	16 (22.22%)	18 (31.03%)	24 (47.06%)	
Total bilirubin (mg/dL)	1.51 ± 2.46	1.15 ± 1.31	0.78 ± 0.36	0.22
AST (IU/L)	85.76 ± 121.12	147.27 ± 266.94	22.45 ± 6.23	<0.01
ALT (IU/L)	125.58 ± 207.68	223.91 ± 357.69	22.05 ± 9.41	<0.01
Hb (g/dL)	14.48 ± 1.85	14.18 ± 1.43	14.10 ± 1.61	0.42
WBC (×1000/μL)	5737.78 ± 2387.54	5376.90 ± 1613.90	5376.75 ± 1513.34	0.50
Platelet (×1000/μL)	134.01 ± 50.28	166.03 ± 41.15	212.52 ± 57.28	<0.01
INR	1.21 ± 0.25	1.12 ± 0.21	1.05 ± 0.13	<0.01
HBV DNA (IU/mL)	5,600,073.33 ± 218,744.21	11,559,255.23 ± 2,979,445.83	2.17 ± 3.71	<0.01
AFP (ng/mL)	13.34 ± 22.64	15.91 ± 51.08	2.43 ± 1.61	0.10
Liver angle (°)	37.74 ± 7.81	35.98 ± 6.56	39.09 ± 7.25	0.10
Liver size	6.34 ± 1.44	6.93 ± 1.25	7.33 ± 1.52	<0.01
Spleen size (cm)	10.79 ± 2.21	9.09 ± 1.52	8.69 ± 0.98	<0.01
PC/SD ratio	1329.08 ± 656.81	1880.58 ± 549.35	2477.22 ± 692.21	<0.01
Follow-up (mo)	48.48 ± 25.73	58.78 ± 32.79	61.75 ± 30.20	<0.01

All data are presented as mean ± standard deviation.
AFP = α-fetoprotein; ALT = alanine transaminase; AST = aspartate transaminase; CHB = chronic hepatitis B; Hb = hemoglobin; HBV = hepatitis B virus; INR = international normalized ratio; PC/SD = platelet count/spleen diameter; WBC = white blood cells.

surprising that cirrhotic patients show much larger decreases in splenic size during NUC therapy. A lower PC/SD ratio is related to higher chances of esophageal varices [14,15]. Therefore, the increased PC/SD ratio during NUC therapy implies improvement of portal hypertension and liver fibrosis.

In our study population, 20% of cirrhotic and 23% of noncirrhotic patients have acute reactivation of CHB with AST levels more than five times the upper normal limit prior to NUC therapy. The spleen is often enlarged during the late phase of acute hepatitis because of congestion and enhanced immune response [28,29]. In this study, we observed the gradual decrease in spleen size during NUC therapy. We did not observe the development of splenomegaly after the acute reactivation of CHB. Conventional sonographies are operator dependent. We included the patients with sonographies performed by the same operator to avoid interobserver variations and performed at least three reproducible spectral patterns to minimize the intraobserver variations. However, the limitation of possible intraobserver variations cannot be excluded.

Table 2 Comparison of clinical characteristics among three groups at endpoint.

	Cirrhosis (n = 72)	Noncirrhosis (n = 58)	Nonreplicative carrier (n = 51)
Total bilirubin (mg/dL)	1.24 ± 3.11	0.77 ± 0.35	0.73 ± 0.34
AST (IU/L)	32.69 ± 26.01*	27.57 ± 7.90*	22.72 ± 7.86
ALT (IU/L)	35.34 ± 36.33*	36.31 ± 61.77*	23.43 ± 19.20
Hb (g/dl)	14.56 ± 2.10	16.79 ± 16.91	13.99 ± 1.93
WBC (×1000/μL)	5924.66 ± 2193.62	5415.66 ± 1317.50	5866.34 ± 1508.69
Platelet (×1000/μL)	160.91 ± 52.22*	189.66 ± 46.16*	212.98 ± 46.38
INR	1.04 ± 0.25*	0.96 ± 0.06*	0.97 ± 0.07
AFP (ng/mL)	3.75 ± 3.73*	2.62 ± 1.53	2.66 ± 1.37*
HBV DNA (IU/mL)	20.53 ± 148.46	131.47 ± 185.18	1.87 ± 6.93
Liver edge (°)	44.03 ± 8.82*	39.16 ± 7.25*	39.37 ± 7.86
Liver size (cm)	7.52 ± 1.55*	7.62 ± 1.40*	7.50 ± 1.58
Spleen size (cm)	9.90 ± 2.16*	8.51 ± 1.44*	8.49 ± 1.08
PC/SD ratio	1741.07 ± 790.89*	2298.87 ± 683.04*	2552.33 ± 634.40

All data are presented as mean ± standard deviation.
*$p < 0.05$ as compared with baseline data.
AFP = α-fetoprotein; ALT = alanine transaminase; AST = aspartate transaminase; Hb = hemoglobin; HBV = hepatitis B virus; INR = international normalized ratio; PC/SD = platelet count/spleen diameter; WBC = white blood cells.

Table 3 Changing percentage of clinical characteristics among three groups.

	Cirrhosis (n = 72)	Noncirrhosis (n = 58)	HBV carrier (n = 51)	p
Liver edge	12.92 ± 13.43%	6.74 ± 12.07%	0.26 ± 8.57%	<0.001
Spleen size	−8.16 ± 7.06%	−6.13 ± 5.12%	−2.15 ± 7.24%	<0.001
Liver size	19.93 ± 19.03%	7.04 ± 13.96%	0.130 ± 0.48%	<0.001
PC/SD ratio	22.94 ± 17.72%	16.92 ± 11.51%	3.30 ± 23.75%	<0.001

All data are presented as mean ± standard deviation.
HBV = hepatitis B virus; PC/SD = platelet count/spleen diameter.

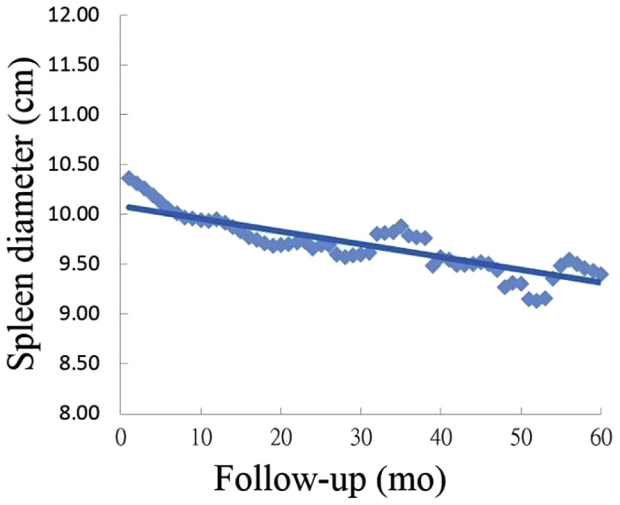

Figure 4 Moving average curve of reduced spleen size in cirrhotic patients during nucleos(t)ides analogue (NUC) therapy.

Furthermore, we observed the significant increase in liver size and angle in patients with cirrhosis during NUC therapy. The increase in liver size and angle indicates the occurrence of hepatic hypertrophy and regeneration [30,31], a phenomenon secondary to the termination of HBV-related hepatic injury by NUCs.

To our understanding, this is the first report to use noninvasive ultrasonographic parameters to monitor the effect of antiviral therapy in HBV-related cirrhosis. The present study has several limitations, such as the retrospective nature of the data and the intraobserver variation during long-term follow-up.

In conclusion, ultrasonography is useful and feasible to evaluate the spleen and liver size in surveillance of patients with CHB. Ultrasonography is practical for clinicians to monitor changes in liver fibrosis and regeneration during NUC treatment in patients with CHB.

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