Clinical efficacy of treated chronic hepatitis B patients with low-level viremia

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Research Article

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Abstract

Objective To compare the efficacy of switching to nucleos (t) ide analogues and continuing to use nucleos (t) ide analogues in patients with chronic hepatitis B with low-level viremia.

Methods From July 2020 to October 2022, 130 patients with chronic hepatitis B who developed low-level viremia after 48 weeks of nucleos (t) ide analogues were retrospectively included in the Affiliated Hospital of Qingdao University, including 59 patients in the changed group and 71 patients in the unchanged group. After propensity score (PSM), 30 patients in the changed group and 30 patients in the unchanged group were retrospectively included. The primary outcome measures were complete virologic response rate (CVR) and HBV DNA load reduction at week 24.Secondary outcome measures were HBsAg clearance rate, HBeAg negative rate and HBeAg seroconversion rate; ALT, AST, TBIL levels; serum phosphorus, creatine kinase, renal function and incidence of liver cirrhotic and cancer.

Results At 24 weeks, the CVR rate was 7 (23.3%) in the unchanged group and 15 (50%) in the changed group , and the difference between the two groups was statistically significant ($P < 0.05$). The decrease of HBV DNA load (log10 IU/mL) was 0.2 (0.05, 1.04) and 1.08 (0.37.1.36) in the unchanged group and the changed group, respectively, and the difference between the two groups was statistically significant ($P < 0.05$).However, there was no significant difference in HBsAg clearance rate, HBeAg negative conversion rate, HBeAg seroconversion rate, ALT, AST, TBIL, eGFR, urine protein, serum phosphorus, creatine kinase and incidence of liver cirrhosis and cancer, between the two groups ($P > 0.05$).

Conclusion For patients with chronic hepatitis B low-level viremia treated with nucleos (t) ide analogues, CVR rate and HBV DNA load decrease are superior to those without dressing change after nucleos(t) ide analogues replacement.

Background

Chronic hepatitis B (CHB) is a chronic inflammatory disease of the liver caused by persistent infection with hepatitis B virus (HBV)(1).The introduction of hepatitis B vaccine and effective mother-to-child blocking have greatly reduced the HBV infection rate. However, according to WHO, there are currently about 257 million chronic HBV infections worldwide, and about 887,000 people die of HBV infection each year worldwide, with cirrhosis and primary hepatocellular carcinoma (HCC) accounting for 30% and 45% of mortality, respectively (1).Active and effective antiviral therapy can significantly reduce the morbidity and mortality of cirrhosis and HCC (2).Current first-line nucleos (t) ide analogues (NAs) are characterized by high potency and low resistance, however, patients with persistent or intermittent low-level viremia (LLV, HBV DNA between 10 and 2000 IU/mL (3)) are common in clinical practice during long-term use. LLV may promote the development of adverse clinical outcomes such as virological breakthrough, drug resistance, liver fibrosis, and hepatocellular carcinoma (4–6).However, it remains controversial to continue the use of the original NAs antiviral or replace analogues after LLV in patients with treated chronic hepatitis B. This study is a real-world retrospective study to evaluate the efficacy of switching to

NAs and continuing the original NAs in patients with LLV by comparing the changed group with the unchanged group.

Methord

Subiects

This study uses the method of retrospective cohort study, and 130 outpatients with liver disease who visited the Affiliated Hospital of Qingdao University from July 2020 to October 2022 were collected. The following inclusion criteria were met: 1. CHB patients who met the diagnostic criteria and treatment criteria of the *The guidelines of prevention and treatment for chronic hepatitis B (2019 version)* (1) and had HBV DNA load between 10 and 2000 IU/mL for more than 48 weeks of oral ETV antiviral therapy; 2. aged 18 years or older; and ; 3. no clear genetic mutations with NAs. Exclusion criteria : 1. Patients who have currently and previously used interferon therapy; 2. Patients with HCV, HDV, HIV infection; 3. Patients with other liver diseases, including autoimmune liver disease, drug-induced liver injury, moderate to severe fatty liver and alcoholic liver disease; 4. Patients with decompensated cirrhosis (such as combined significant ascites, variceal bleeding or encephalopathy) and liver cancer and other cancers; 5. Patients with moderate to severe renal failure; 6. Pregnant or breastfeeding women; 7. Poor clinical compliance.

Study design

130 patients were subjected to propensity score (PSM), 30 patients in the changed group and 30 patients in the unchanged group after matching. In the unchanged group, the original antiviral analogues were continued, including entecavir (ETV) in 26 patients (86.7%) and tenofovir disoproxil fumarate (TDF) in 4 patients (13.3%). In the changed group, 22 patients (73.3%) switched to tenofovir alafenamida fumarate (TAF); 2 patients (6.6%) to TDF; 4 patients (13.3%) to ETV + TAF; and 2 patients (6.6%) to tenofovir amibufenamide tablets (TMF). Patients treated with ETV received 0.5 mg once daily; those treated with TDF received 300 mg once daily; those treated with TAF received 25 mg once daily; those treated with TMF received 25 mg once daily; and those treated with ETV + TAF received 0.5 mg ETV + 25 mg TAF daily. ETV was administered on an empty stomach, and TDF, TAF, and TMF were administered with meals.

Outcome measures and detection methods

HBV DNA, five items of hepatitis B, ALT, AST, TBIL, serum phosphorus, serum calcium, creatine kinase, creatinine and glomerular rate (eGFR) were collected from LLV patients at baseline and week 24. Serum HBV DNA was quantified by imported Abbott reagent, PCR Real Time (lower limit of detection < 10 IU/ml), Roche reagent (electrochemiluminescence) for five items of hepatitis B, and enzyme-linked immunosorbent assay for liver function. Cirrhosis and liver cancer were identified by abdominal ultrasound and abdominal CT/MRI.

Statistical methods

SPSS 25.0 statistical software was used for data analysis and GraphPad Prism8 software was used for mapping. Measurement data conforming to normal distribution were analyzed by two independent samples t test and expressed as mean ± standard deviation ($\bar{x} \pm s$). Measurement data with skewed distribution were analyzed by non-parametric test (Kruskal-Wallis test) and presented as median (interquartile range) [M (P25, P75)]. Enumeration data were compared using χ^2 test and Fisher exact test. $P < 0.05$ was significantly different. PSM applies SPSS 25.0 with a match tolerance of 0.01.

Results

1.Baseline characteristics: 130 patients who met the inclusion and exclusion criteria were compared and analyzed for gender, age, liver cirrhosis, duration of NAs use, Family history of hepatitis B cirrhosis and HCC, HBV DNA, HBeAg positive rate, ALT, AST, TBIL, serum creatinine, eGFR, serum phosphorus, serum calcium and creatine kinase at the start of the protocol. There were no significant differences in gender, age, liver cirrhosis, ALT, AST, TBIL, serum creatinine, eGFR, serum phosphorus, serum calcium and creatine kinase ($P > 0.05$), and there were significant differences in the time of NAs use, family history, HBV DNA, and HBeAg positive rate between the two groups ($P < 0.05$) (Table 1). A propensity score (PSM) was therefore performed to balance the deviation between the two groups. After PMS, there were no significant differences in gender, age, liver cirrhosis, duration of antiviral drug use, family history, HBV DNA, HBeAg positive rate, ALT, AST, TBIL, serum creatinine, eGFR, serum phosphorus, serum calcium and creatine kinase between the two groups ($P > 0.05$) (Table 2).

Table 1
Comparison of baseline (0 weeks) data between the unchanged group and the changed group

	Unchanged group(n = 71)	Changed group(n = 59)	Statistical value	*P*
Male, n(%)	54(76.1)	45(76.3)	0.001	0.977
Age, year	41.3 ± 10.1	43 ± 9.2	0.996	0.321
Cirrhosis, n(%)	24(33.8)	14(23.7)	1.581	0.209
Time of NAs, year	2.0(1.5,5.0)	2.0(1.0,3.2)	2.013	0.044
Family history, n(%)	17(23.9)	24(40.7)	4.179	0.041
HBV DNA (log10IU/mL)	1.39(1.18,1.68)	2.07(1.51,2.78)	4.935	< 0.001
HBeAg positive, n (%)	42(59.2)	48(81.4)	0.456	0.006
ALT, U/L	26.3(19,39.8)	31.1(21.2,52.8)	1.569	0.117
AST, U/L	21.5(18.1,26.1)	21.6(18.1,29.8)	0.483	0.629
TBIL, μmol/L	20(16.2,25.9)	20(14.4,24.9)	0.781	0.435
ALB, g/L	46.1(44.45,47.8)	45.3(44,47.1)	1.396	0.163
PLT, $\times 10^9$/L	193.1 ± 66.9	201.1 ± 62.7	0.705	0.482
CREA, μmol/L	92.3 ± 11.8	92.3 ± 13.2	0.003	0.998
BUN, mmol/L	4.8 ± 1.1	5.0 ± 1.1	0.900	0.370
eGFR, mL/min/1.73m^2	84.3(76.0,90.7)	81.95(75.0,93.3)	0.192	0.898
Urine albumin, n (%)	10(14.1)	14(23.7)	1.991	0.158
Phosphorus, mmol/L	1.06 ± 0.15	1.04 ± 0.16	0.981	0.328
Calcium, mmol/L	2.35 ± 0.11	2.34 ± 0.08	0.198	0.844
Creatine kinase, U/L	120(82,140)	108(73.3,144.9)	0.678	0.498

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, plasma albumin; PLT, platelets; CREA, serum creatinine; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

Table 2 Comparison of baseline (0 weeks) data between the unchanged group and the changed group after PSM

	Unchanged group(n=30)	Changed group(n=30)	Statistical value	*P*
Male, n (%)	20(66.7)	22(73.3)	0.317	0.573
Age, year	42.0±9.9	42.7±8.1	0.299	0.766
Cirrhosis, n (%)	6(20)	12(33.3)	1.364	0.243
Time of NAs, year	2(1.38,5)	2(1,4)	0.679	0.497
Family history, n (%)	10(33.3)	12(40)	0.287	0.592
HBV DNA (log10IU/mL)	1.54(1.37,2.02)	1.66(1.35,2.15)	0.148	0.882
HBeAg positive, n (%)	24(80)	21(70)	0.800	0.371
ALT, U/L	25.5(20.5,39.9)	24.9(18.8,46.0)	0.177	0.859
AST, U/L	21.9(19.5,25.9)	19.5(16.68,30.5)	0.835	0.403
TBiL, μmol/L	19.6(15.8,25.4)	19.8(15.9,25.5)	0.177	0.859
ALB, g/L	45.7±2.7	42.7±8.1	0.336	0.738
PLT, $\times 10^9$/L	197.1±55.2	194.1±72.0	0.181	0.857
CREA, μmol/L	89.1±13.6	92.9±13.0	1.102	0.275
BUN, mmol/L	4.5±0.7	4.9±1.1	1.536	0.131
eGFR, mL/min/1.73m^2	85.5±13.9	82.8±11.6	0.815	0.418
Urine albumin, n(%)	7(23.3)	5(16.7)	0.417	0.519
Phosphorus, mmol/L	1.06±0.18	1.06±0.14	0.131	0.896
Calcium, mmol/L	2.34±0.12	2.36±0.09	0.719	0.475
Creatine kinase, U/L	109.3(77.0,136.5)	116.3(75.3,164.8)	0.651	0.515

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, plasma albumin; PLT, platelets; CREA, serum creatinine; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

2 Laboratory parameters at week 24 in the two groups:

2.1 Virological parameters: complete virological response (CVR, defined as serum HBV DNA level lower than the lower line of detection 10 IU/mL) 7 patients (23.3%) in the unchanged group and 15 patients (50%) in the changed group, and the difference between the two groups was statistically significant ($P < 0.05$). For HBV DNA load decrease, the median values were 0.2 (0.05, 1.04) log10IU/mL and 1.08

(0.37.1.36) log10IU/mL in the unchanged group and the changed group, respectively, and the difference between the two groups was statistically significant ($P < 0.05$) (Figure 1). HBsAg loss was not achieved in either group. HBeAg negative conversion rate and HBeAg seroconversion rate were 0 and 2 cases (9.5%) in the unchanged group and changed group, respectively, but there was no significant difference between the two groups ($P > 0.05$) (Table 3).

2.2 Biochemical indicators of liver function: There was no significant difference in ALT, AST and TBIL levels between the two groups ($P > 0.05$) (Table 4).

2.3 Renal function, serum phosphorus and creatine kinase: The mean ± standard deviation of eGFR (mL/min/1.73 m^2) level in the unchanged group and changed group were 83.9 ± 12.3 and 84.0 ± 10.1, respectively, and there was no significant difference between the two groups ($P > 0.05$). There were 9 cases (30%) of positive urine protein in the unchanged group and 3 cases (10%) in the changed group. The positive rate of urine protein in the dressing change group was lower than that in the unchanged group, but there was no significant difference between the two groups ($P > 0.05$). Serum phosphorus and creatine kinase were not significantly different between the two groups ($P > 0.05$) (Table 5).

2.4 Incidence of liver cirrhosis and HCC: No liver cirrhosis or HCC occurred in the two groups.

Table 3
Comparison of virological parameters between the unchanged group and the changed group at week 24

	Unchanged group	Changed group	Statistical value	*P*
CVR, n (%)	7/30(23.3)	15/30(50.0)	4.593	0.032
HBV DNA decrease (log10IU/mL)	0.20(0.05,1.04)	1.08(0.37,1.36)	2.839	0.005
HBsAg loss, n (%)	0	0		
HBeAg loss, n (%)	0/24	2/21(9.5)		0.212
HBeAg seroconversion , n (%)	0/24	2/21(9.5)		0.212
Abbreviations: CVR, complete virological response; HBV DNA, hepatitis B virus deoxynbonucleic acid; HBeAg, hepatitis B e antigen.				

Table 4
Comparison of biochemical indicators of liver function between the unchanged group and the changed group at week 24

	Unchanged group(n = 30)	Changed group(n = 30)	Statistical value	*P*
ALT, U/L	26.05(20.8,35.1)	29.6(20.1,39.9)	0.769	0.442
AST, U/L	22.2(19.0,24.0)	19.9(18.0,27.4)	0.481	0.631
TBIL, μmol/L	19.35(12.8,24.6,)	18.7(15.5,26.5)	0.591	0.554
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin.				

Table 5
Comparison of renal function, serum phosphorus and creatine kinase between the n unchanged group and the changed group at week 24

	Unchanged group(n = 30)	Changed group(n = 30)	Statistical value	*P*
eGFR, mL/min/1.73m^2	83.9 ± 12.3	84.0 ± 10.1	0.033	0.974
Urine albumin, n(%)	9(30)	3(10)	3.75	0.053
Phosphorus, mmol/L	1.08(0.90,1.22)	1.02(0.89,1.16)	0.851	0.395
Creatine kinase, U/L	100.5(67.8,127.8)	98.25(75.2,157.2)	0.370	0.712
Abbreviations: eGFR, estimated glomerular filtration rate.				

Discussion

During the treatment of chronic hepatitis B, it has been found that some patients with long-term HBV DNA below the lower line of detection (< 2000 IU/mL) still develop cirrhotic or liver cancer after regular antiviral therapy. With the advent of highly sensitive DNA detection technology, studies have shown that about 20%-30% of patients regularly taking NAs (7-10) 2have LLV, and the presence of LLV may increase the incidence of cirrhosis, liver cancer and drug resistance in patients with hepatitis B (4-6).Eliminating LLV to achieve CVR reduces the incidence of these adverse clinical outcomes (11).However, the treatment of chronic hepatitis B LLV is still controversial, and the *Expert opinion on expanding anti-HBV treatment for chronic hepatitis B published in 2022* (12) states that CHB patients who have been treated with antiviral therapy for more than 48 weeks but still have low-level viremia can refer to the management of poor response in each guideline; after excluding compliance and detection errors, those who use ETV switch to or add TDF or TAF, those who use TDF or TAF switch to or add ETV, and those who use TDF or TAF can also consider combined Peg IFN-a therapy. *The AASLD 2018 hepatitis B guidance* (3) state that patients with persistent LLV treated with ETV or TDF can continue ETV or TDF alone, switch to another NAs monotherapy for patients with virological breakthrough, or add another antiviral drug without cross-resistance .Compared with the Expert opinion on expanding anti-HBV treatment for chronic hepatitis

B, *the AASLD 2018 hepatitis B guidance*(3), in addition to recommending switching to or combining antiviral analogues, the former recommends continuing the use of the original NAs, and because there are some differences between the two guidelines, we did further research.

In this study, we observed the efficacy of changed and unchanged for LLV after antiviral therapy with different NAs in general. Patients who had been taking NAs for 48 weeks were included in the study, with ETV and TDF, and switched to single or combined analogues. At week 24, the CVR rate, the main outcome measure, was 7 cases (23.3%) in the unchanged group and 15 cases (50%) in the changed group, and the difference between the two groups was statistically significant ($P < 0.05$).The decrease of HBV DNA load was 0.2 (0.05,1.04)log10IU/mL and 1.08 (0.37,1.36) log10IU/mL in the unchanged group and the changed group, respectively, and the difference between the two groups was statistically significant ($P < 0.05$).In terms of CVR rate and HBV DNA decrease value, the effect of dressing change is better than that of no dressing change, which may be due to different drug action sites and different drug resistance genes (13, 14), resulting in different antiviral effects. When LLV occurs after 48 weeks of antiviral therapy with NAs, although CVR also occurs in some patients who continue to use the original NAs, the latter is virologically superior and can achieve CVR in a greater proportion than switching to or combining with other NAs. In the secondary outcome measures, HBsAg was not eliminated, HBeAg loss rate and HBeAg seroconversion rate were observed in both groups at 24 weeks, 0 and 2 patients (9.5%) in the unchanged group and the changed group, respectively, although the changed group was higher than the unchanged group, there was no significant difference between the two groups ($P > 0.05$).Thus, for HBsAg loss, NAs alone are less effective. Studies have shown that combined interferon can improve HBsAg loss (15-17), but its widespread use is limited due to the relatively large side effects of interferon, small and expensive dominant population (1, 18-20), and patients are recommended to use interferon in combination if they belong to the dominant population. There was no significant difference in the incidence of liver cirrhosis and HCC between the two groups at 24 weeks ($P > 0.05$), which may be due to the short observation time, even if there was a difference for a short time. There was no significant difference in ALT, AST, TBIL, eGFR, urine protein, serum phosphorus and creatine kinase between the two groups ($P > 0.05$), which may be related to the fact that ALT and AST were generally in the normal range in the observation subjects included in this study, and transaminase decreased insignificantly even if CVR was achieved. At 24 weeks, there was no significant difference in renal function and serum creatine kinase between the two groups. On the one hand, the possible reason was that the analogues used by the patients were first-line analogues, and the side effects of the analogues themselves were small. On the other hand, the possible reason was that the observation cycle was short, which could not be reflected even if there was a difference in a short time.

Conclusion

In conclusion, for patients with previously treated chronic hepatitis B LLV, switching to NAs for CVR rate and HBV DNA load reduction is superior to no dressing change, and switching to antiviral analogues is recommended if patients are allowed by economic conditions. However, for the long-term advantages

and disadvantages caused by dressing change, it still needs a large sample, long-term, multicenter clinical review and prospective study.

Abbreviations

ALB, plasma albumin

ALT, alanine aminotransferase

AST, aspartate aminotransferase

BUN, blood urea nitrogen

CHB, chronic hepatitis B

CREA, serum creatine

CVR, complete virological response

cccDNA, covalently dosed circular DNA

ETV, entacvir

eGFR, estimated glomerular filtration rate

HBV, hepatitis B virus

HBeAg, hepatitis B e antigen

HBV DNA, hepatitis B virus deoxynbonucleic acid

HCC, hepatocellular carcinoma

LLV, low-level viremia

NAs, nucleos (t) ide analogues

Peg IFN-a, pegylated interferon alpha-a

PLT, platelet

TAF, tenofovir alafenamide Fumarate

TBIL, total bilirubin

TDF, tenofovir disoproxil fumarate

Declarations

This study informed consent was obtained from all subjects and/or their legal guardian(s) and has been approved by the Ethics Committee of the Affiliated Hospital of Qingdao University, Ethics No.: QYFY WZLL 27858.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare to have no financial and non-financial competing interests related to this work.

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Authors' contributions

Yang Gao and Chunhua Bi participated in the design of this study, and Yang Gao, Bibi Xuan ,Yuling Yang, Yujian Cui and Wenjun Huang participated in case collection. Gao Yang performed the statistical analysis and writing of this study, and Chunhua Bi proofread this paper.All authors reviewed the manuscript.

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Figures

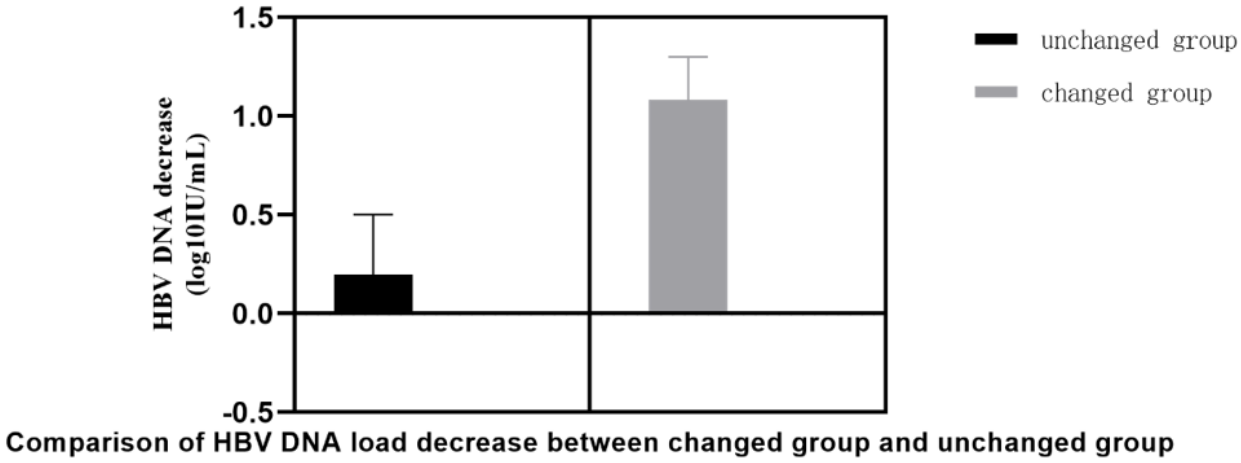

Figure 1

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