Association of Dyslipidemia With Nucleoside Analogue Treatment in HBeAg-Positive Chronic Hepatitis B Patients

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Research Article

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Abstract

Background

The prevalence of dyslipidemia in China is increasing annually. Current studies suggest that dyslipidemia affects the antiviral efficacy of hepatitis C virus (HCV) therapies. Recent studies have shown that serum lipids influence the response rates of chronic hepatitis B patients receiving PEGylated interferon-alpha (Peg IFN- α) treatment. However, the role of dyslipidemia in the efficacy of nucleoside (acid) analogues in chronic hepatitis B patients has not been determined.

Methods

From January 2010 to December 2013, data from 179 treatment-naive patients with chronic hepatitis B (CHB) who were hepatitis B e antigen (HBeAg)-positive and visited the first affiliated hospital of Wenzhou Medical University were collected. Amongst them, 68 patients were diagnosed with CHB complicated with dyslipidemia (dyslipidemia group) whilst 111 patients comprised the lipid control group. Three treatment strategies were performed amongst the 179 CHB patients over a 5 year period. Treatments included combination therapy of lamivudine (LAM) plus adefovir dipivoxil (ADV), telbivudine (LdT) monotherapy or entecavir (ETV) monotherapy. Serum assessments, blood biochemistry, HBV serological markers, HBV DNA before treatment and HBeAg serological conversion and virological responses at different time points after treatment were compared between the two groups. Measurement data were compared using t tests, whilst enumeration data were compared using χ^2 tests. Correlation analysis was performed using binary Logistic regression analysis.

Results

The rates of HBeAg seroconversion in the dyslipidemia group at years 1, 2, 3 and 4 were 10.3%, 13.2%, 17.6% and 22.1%, respectively, which were not significantly lower than those of the lipid control group 11.7%, 16.2%, 18.0% and 33.3%, ($\chi^2 = 0.085, 0.293, 0.004$ and 2.601 , respectively; $R > 0.05$). However, the rates of HBeAg seroconversion in the dyslipidemia group were significantly lower than those of the lipid control group at year 5 (27.9% vs 43.2%, $\chi^2 = 4.216$, $R < 0.05$). Univariate logistic regression analysis showed significant differences in sex PTA, ALT, AST, CR and LDL-C. Multivariate regression analysis demonstrated that dyslipidemia (OR=1.993, $R=0.038$), and male gender (OR=2.317, $R=0.029$) were risk factors associated with HBeAg seroconversion.

Conclusions

During antiviral therapy, dyslipidemia affects HBeAg seroconversion in CHB patients treated with nucleoside (acid) analogues but does not affect the virological response.

Background

Chronic hepatitis B virus (HBV) infection is a major risk factor for hepatocellular carcinoma (HCC) [1]. In the 2010 Global Burden of Disease study, HBV infection ranked within the top global health priorities and was the 10th cause of death (786 000 deaths per year) [2]. Chronic HBV infection remains a serious global health problem more than 292 million individuals infected [3]. In China, patients infected with chronic HBV account for nearly half of global disease burden. Specifically, even with the free administration of the hepatitis B vaccine, approximately 93 million infected with chronic HBV in China, including ~20 million patients with chronic hepatitis B (CHB) [4]. Currently, no effective therapies exist that lead to a complete recovery of HBV infection. Once entering liver cells, HBV delivers its covalently closed circular DNA (cccDNA) genome, of which the long half-life, self-renewal capacity, and current lack of direct therapeutics lead to lack of elimination of cccDNA. However, the persistent existence of cccDNA integrating HBV DNA and the impairment of innate and specific immunity contribute to the difficulties in clearing chronic HBV infection.

HBeAg, a non-structural protein that is encoded by pre-C/C gene, is a serum antigen marker after hepatitis B infection. HBeAg reflects the active replication of the hepatitis B virus, with a solid infectious. After HBeAg seroconversion, some patients were in the low replication phase, characterized by normal serum ALT concentration and minimal liver histological changes, suggesting slowed liver damage [5]. Consequently, seroconversion is the target of CHB patients with HBeAg positive.

Interferon (IFNs) and nucleoside (acid) analogues (NAs) can efficiently inhibit HBV replication and reduce the incidence of liver cirrhosis, hepatic failure and hepatocellular carcinoma (HCC) [6]. NAs inhibit the reverse transcription of pre-genome RNA and HBV DNA synthesis in the cytoplasm, but do not directly influence the viral cccDNA. Interferon promotes the host immune defenses to HBV the precise mechanisms of which remain unclear. Recent studies show that, compared to NAs, IFNs promote the degradation of cccDNA and lead to epigenetic modifications in the transcription of cccDNA [7]. However, the therapeutic applications of common IFN-and PEG IFN- are limited and their use is prohibited in patients with uncompensated cirrhosis of the liver, the acute exacerbation of chronic hepatitis, autoimmune disease or mental illness. Nucleoside analogues are widely used in China, but show low efficacy.

With the development of the national economy, the prevalence of dyslipidemia in the Chinese population is increasing annually. Dyslipidemia generally refers to increased cholesterol (TC) and/or triglyceride (TG) levels in the serum, and refers to various dyslipidemia states including low-high density lipoprotein cholesterol (HDL-C) blood symptoms [8]. To-date, lipid metabolism as a consequence of chronic HBV infection is well characterized [9-11]. The expression of HBV in transgenic mice alters lipid metabolism and induces oxidative stress in the liver [10]. HBV infection can induce the expression of genes involved in cholesterol synthesis and promote cholesterol production [12]. Additionally, HBV X protein inhibits the secretion of apolipoprotein B (Apo-B) and promotes the activity of fatty acid synthetase [13,14]. In turn, dyslipidemia influences HBV infection, which depends on cholesterol in the virus envelope [15-17]. Furthermore, an increased body mass index in CHB patients is related to hepatic steatosis [16]. Cholesterol promotes HBV infection [17]. To-date, it is known that dyslipidemia is related to the

therapeutic response of patients with chronic hepatitis C to PEG-IFN [18,19]. LDL- cholesterol (LDL-C) is a predictor of an early and sustained virological response. Recent studies have shown that dyslipidemia affects the efficacy of IFN towards patients with CHB [20] but studies on the effects of dyslipidemia on the efficacy of nucleoside (acid) analogues in CHB patients are limited. This study retrospectively analyzed the effects of dyslipidemia on the antiviral efficacy of nucleoside (acid) analogues in HBeAg-positive CHB patients.

Methods

Patient data

We selected a total of 179 newly treated CHB patients with HBeAg positive hospitalized in the First Affiliated Hospital of Wenzhou Medical University from January 2010 to December 2013, who were following the guidelines for the prevention and treatment of chronic hepatitis B (2015) [21]. The study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, and the informed consent of all patients was obtained.

Inclusion criteria: age ≥ 16 years old; serum HBV DNA ≥ 20000 IU/mL; HBsAg positive, duration > 6 months; HBeAg positive and anti-HBe negative. Exclusive criteria: previously received antiviral, immunomodulatory drugs or corticosteroid therapy; liver diseases caused by other causes, the elevated ALT caused by non-liver diseases; HCV, HDV or HIV infection; decompensated liver diseases history or stage. According to the dyslipidemia complication, patients were divided into two groups, including 68 subjects with dyslipidemia and 111 subjects without dyslipidemia. The diagnostic criteria for dyslipidemia followed the Prevention Guidelines of dyslipidemia in Chinese Adults (2016 Revision) [8]. Treatment regimens included oral lamivudine (Heptodin, GlaxoSmithKline Pharmaceutical Co., Ltd.) 100mg qd combined with adefovir dipivoxil (Hepsera, GlaxoSmithKline Pharmaceutical Co., Ltd.) 10mg qd; Or Telbivudine monotherapy 600mg qd (Sebivo, Beijing Novartis pharmaceutical co., Ltd.); or entecavir monotherapy (Baraclude, Sino-American Shanghai Squibb Pharmaceutical Co., Ltd.) 0.5mg qd; 5-years of treatment. If the drug was discontinued or other drugs were used during the treatment, the case was withdrawn from the study.

Detection indicator

Venous blood was drawn for various blood tests after fasting overnight for 12 h. Lipid indexes, including TC (2.44-5.17 mmol/L), TG (0.4.-1.70 mmol/L), LDL-C (2.07-3.10 mmol/L), HDL-C (1.29-1.55 mmol/l) and biochemical indexes including ALT (7-40U/L), AST (13-35U/L), ALP (50-135U/L), r-GT(7-45U/L), were measured using standard techniques. Semi-quantitative analysis of HBV serological marker including HBsAg and HBeAg was performed by ECLIA (electrochemiluminescence immunoassay). In addition, quantitative detection of HBV DNA was performed. The HBeAg seroconversion rates and virological response rates from 1-5 years of treatment were calculated. HBeAg seroconversion was analyzed through the detection of anti-HBE and HBeAg.

Statistical analysis

SPSS 25.0 statistical software was used for all data analysis. Measurement data are shown as the mean $\pm$ SD using t tests. Enumeration data were assessed by the rate utilizing χ^2 test, the corrected χ^2 test, or Fisher's exact test. Correlation analysis was performed through Binary Logistic Regression analysis. $P < 0.05$ indicated statistical significance.

Results

Baseline data

A total of 179 HBeAg-positive CHB patients were primarily treated with lamivudine combined with adefovir dipivoxil, either telbivudine monotherapy or entecavir monotherapy for 5 years. Amongst them, 14 subjects were treated with lamivudine combined with adefovir dipivoxil, 78 subjects were treated with telbivudine monotherapy, and 87 subjects were treated with entecavir monotherapy. The study subjects were comprised of 143 males and 36 females, aged 16 to 75, with an average age of 40.4 ± 12.0 . In total, 17 subjects had hypercholesterolemia, 21 subjects had hypertriglyceridemia and 30 subjects had mixed hyperlipidemia. Table 1 shows that the MBI, TC, TG, LDL-C of patients in the dyslipidemia group were significantly higher than those without dyslipidemia. However, no significant differences in age, sex, ALT, AST, HBsAg, HBeAg, HBV DNA treatment regimens or other indicators were observed.

Comparison of HBeAg seroconversion rates after antiviral treatment of nucleoside (acid) analogues

Table 2 shows the seroconversion rates of the HBeAg group with dyslipidemia as 10.3%, 13.2%, 17.6% and 22.1%, respectively from years 1-4, which were lower than those diagnosed in the lipid control group (11.7%, 16.2%, 18.0% and 33.3%, respectively) but lacking a significant difference ($\chi^2 = 0.085, 0.293, 0.004, 2.601, P > 0.05$). In the 5th year, the HBeAg seroconversion rates in the dyslipidemia group were 27.9%, which were significantly lower than the 43.2% observed in the lipid control group ($\chi^2 = 4.216, P < 0.05$).

Comparison of virological response rates of the nucleoside analogues following antiviral treatment

The virological response rates of the HBV DNA dyslipidemia group were 63.2%, 69.1%, 76.5%, 83.8%, 89.7% from years 1-5 respectively, which was lower than the lipid control group (69.4%, 74.8%, 83.8%, 92.8% and 95.5%, respectively) but the differences were not significant ($\chi^2 = 0.718, 0.679, 1.466, 3.573, 1.429, P > 0.05$), (Table 3).

Comparison of baseline data, virological response and HBeAg seroconversion

Amongst the subjects, 14 were treated with lamivudine combined with adefovir dipivoxil, 78 were treated with telbivudine monotherapy and 87 were treated with entecavir. No differences in ALT, AST, HBsAg, HBeAg or HBV-DNA in the three groups of patients receiving the various treatment regimens were observed. The HBV DNA virological response rates as well as HBeAg negative rates in the three groups also showed no significant differences (Table 4).

Correlation analysis between dyslipidemia and HBeAg seroconversion

Through single-factor logistic regression analysis, differences in group, gender, PTA, ALT, AST, CR, and LDL-C significantly differed between the groups (OR = 1.965, 2.212, 0.959, 1.003, 1.004, 0.97, 0.668, $p = 0.041, 0.036, 0.004, 0.000, 0.014, 0.022$, respectively, Table 5). The factors influencing HBeAg seroconversion were included in the multivariate logistic regression analysis and suggested that dyslipidemia and male gender were risk factors for HBeAg seroconversion (OR=1.993, 2.317, $P= 0.038, 0.029$).

Discussion

Chronic HBV infection is a major health burden with worldwide infection rates of 3.6%, amongst which 250 to 350 million people are positive for HBsAg which varies according to geographical regions [22,23]. Life-threatening complications such as liver cirrhosis and hepatocellular carcinoma (HCC) arise when chronic viral infections are left undiagnosed or untreated. The availability of a prophylactic vaccine has reduced the emergence of new HBV infections amongst children aged less than 5 years who are most vulnerable to the development of persistent infections [24]. To-date, two therapeutic strategies are approved for the management of chronic HBV infection, namely nucleoside/nucleotide analogues (NAs) and interferon α (IFN- α)/ polyethylene glycol interferon (PEG-IFN) [25].

In China, the prevalence rates of dyslipidemia over the last three decades have significantly increased with the development of China's economy [8]. Dyslipidemia is directly related to poor eating habits, a lack of exercise, and increased age, leading to chronic kidney diseases, cardiovascular disease, diabetes, fatty liver and other diseases. Blood lipid metabolism is influenced by chronic HBV infection [9-11] and dyslipidemia, in turn, influences HBV infection [15-17]. Recent studies suggest that dyslipidemia is related to Peg IFN- α responses in CHB patients [20]. However, studies on the effects of dyslipidemia on the efficacy of nucleoside (acid) analogues in CHB patients are sparse. Therefore, the impact of dyslipidemia on the antiviral efficacy on CHB patients requires further clinical investigations. Consequently, this study explored the effects of dyslipidemia on the antiviral efficacy of nucleoside (acid) analogues on HBeAg-positive CHB patients. Current treatment guidelines recommend Peg IFN- α , entecavir or tenofovir disoproxil as the first choice for primary patients. However, some patients maintain the use of Telbivudine monotherapy or lamivudine combined with adefovir dipivoxil as an antiviral therapy.

We found that the virological response and HBeAg seroconversion rates of the group with dyslipidemia were lower than those of the lipid control group. Specifically, no significant differences in virological response rates at each time point during treatment were observed and no statistical differences in HBeAg seroconversion rates in the first 4 years occurred, leading to statistical differences in HBeAg seroconversion rates in the 5th year. HBeAg seroconversion is associated with progressive reduction of the viral DNA quantification. It is surprising therefore that HBV DNA was not also associated with dyslipidemia status. However, this may be because of the association with only late-HBeAg seroconversion. As revealed through binary logistic regression analysis, dyslipidemia and male gender

are risk factors for HBeAg seroconversion. Dyslipidemia can affect human immune function the specific mechanisms of which are currently lacking. Bile acid promotes the expression of HBV and weakens the antiviral effects of IFN [26]. Furthermore, bile acid originates from cholesterol, allowing us to propose that bile acid metabolism in CHB patients is affected by dyslipidemia, influencing the antiviral effects. Additionally, metabolic stress caused by dyslipidemia leads to harmful immune activation, resulting in high levels of CD4+T cells and lowered HBeAg seroconversion as a consequence of cellular dysfunction [27,28].

Conclusions

In summary, dyslipidemia influences HBeAg seroconversion. As such, controlling blood lipid levels can improve HBeAg seroconversion rates. Consequently, for CHB patients with dyslipidemia, blood lipid levels should be controlled when receiving antiviral therapy, including diet regulation, weight management, and temperance. When required, lipid-altering drugs can improve the seroconversion rates of patients with HBeAg. This study was based on a retrospective analysis that requires confirmation in clinical prospective studies. Furthermore, only a small number of subjects were assessed due to the long follow-up period, potentially introducing study bias.

Abbreviations

ADV: adefovir dipivoxil; Apo-B: apolipoprotein B; cccDNA: covalently closed circular DNA; CHB: chronic hepatitis B; ECLIA : electrochemiluminescence immunoassay; ETV: entecavir; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; HCC:hepatocellular carcinoma; HCV: hepatitis C virus; HDL-C: high density lipoprotein cholesterol; IFNs: Interferon; LAM: lamivudine; LdT: telbivudine; NAs: nucleoside (acid) analogues; Peg IFN- α : PEGylated interferon-alpha; TC: cholesterol; TG: triglyceride.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, and the informed consent of all patients was obtained.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there are no conflicts of interest.

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Authors' contributions

Z.X.,J.W.,X.S.: Conceptualisation; Z.X.,E.Z.: Methodology; J.Z.,L.Z.: Formal Analysis; Z.X.,Z.Z.: Writing – Original Draft Preparation; J.W.,X.S.: Writing – Review and Editing.

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Tables

Table 1. Comparison of baseline characteristics between dyslipidemia and lipid control groups

Baseline Data	Dyslipidemia Group	Lipid Control Group	t/c ² value	R value
	68	111		
Male (n, %)	57	86	0.415	0.520
Age (years)	39.5±11.9	40.9±12.2	0.795	0.428
Combined therapy (n, %)	5	9	0.187	0.911
BMI (kg/m ²)	25.0±3.1	22.4±2.2	5.428	0.000*
WBC (×10 ⁹ /L)	6.3±2.1	5.6±1.4	2.897	0.004*
NE%	0.6±0.1	0.6±0.1	0.138	0.890
NE(×10 ⁹ /L)	3.7±1.7	3.2±1.2	2.586	0.011*
RBC(×10 ¹² /L)	4.8±0.6	4.8±0.5	0.217	0.828
HB (g/L)	147.9±15.7	145.5±14.9	1.048	0.296
RDW (%)	13.4±1.2	13.3±2.8	0.158	0.875
PLT (×10 ⁹ /L)	230.5±78.5	215.2±60.9	1.368	0.174
PT (s)	13.5±0.8	13.4±1	0.715	0.476
PTA (%)	92.2±10.0	92.8±13.3	0.341	0.733
INR	1±0.1	1±0.1	0.180	0.857
F (g/L)	3.1±0.6	3.1±0.9	0.398	0.691
APTT (s)	37.3±4.2	36.8±5.2	0.795	0.428
APTTR	1.0±0.1	1.0±0.2	0.140	0.889
TT (s)	17.1±1.3	17.1±1.5	0.175	0.862
TTR	1.0±0.1	1.0±0.1	0.228	0.820
TB (umol/L)	25.4±58.9	15.1±20.1	1.692	0.092
DBIL (umol/L)	15.3±50.3	7.1±18.1	1.502	0.135
TP (g/L)	75.5±6.2	73.7±6.6	1.889	0.061
A (g/L)	43.9±5.6	44.4±5.3	0.587	0.558
ALT (U/L)	349.1±275.2	297.1±224	1.314	0.191
AST (U/L)	249.1±175	266.7±175.9	0.830	0.408
ALP (U/L)	90±22	84.1±23.2	1.719	0.088

r-GT (U/L)	75.9±56.6	72.5±42	0.430	0.688
FBG (mmol/L)	5.3±1.3	5.4±1.6	0.697	0.487
BUN (mmol/L)	4.8±1.4	4.5±1.1	1.338	0.184
CR (mmol/L)	69.3±12.5	67.6±13.7	0.838	0.403
UA (umol/L)	379.9±105	359.9±99.4	1.257	0.211
TC (mmol/L)	5.5±1.3	4.0±0.7	10.210	0.000*
TG (mmol/L)	2.2±0.8	1.1±0.3	12.633	0.000*
HDL-C (mmol/L)	1.1±0.4	1.1±0.3	0.284	0.777
LDL-C (mmol/L)	3.4±1.0	2.3±0.7	8.574	0.000*
HBsAg S/CO	7557.4±10826.3	5377.3±7487.7	1.494	0.137
HBeAg S/CO	901.5±514.4	777.3±512.9	1.567	0.119
HBV DNA Log ₁₀ IU/ml	7.4±1.2	7.6±1.1	1.114	0.267

Note: *comparison between dyslipidemia and lipid control groups P<0.05

Table 2. Comparison of HBeAg serological conversion rates between dyslipidemia and lipid control groups at different treatment times (number of subjects, %)

Groups	Number of Subjects	HBeAg serological Conversion Rate				
		1 st year	2 nd year	3 rd year	4 th year	5 th year
Dyslipidemia Group	68	7 (10.3)	9 (13.2)	12(17.6)	15(22.1)	19(27.9)
Lipid Control Group	111	13(11.7)	18(16.2)	20(18.0)	37(33.3)	48(43.2)
Test value		0.085	0.293	0.004	2.601	4.216
P value		0.770	0.589	0.950	0.107	0.040*

Note: *comparison between dyslipidemia and lipid control groups P<0.05.

Table 3. Comparison of HBV DNA virological response rates between dyslipidemia and lipid control groups at different treatment times (number of subjects, %)

Groups	Number of Subjects	HBV DNA Virological Response Rate				
		1 st year	2 nd year	3 rd year	4 th year	5 th year
Dyslipidemia Group	68	43(63.2)	47(69.1)	52(76.5)	57(83.8)	61(89.7)
Lipid Control Group	111	77(69.4)	83(74.8)	93(83.3)	103(92.8)	106(95.5)
Test value		0.718	0.679	1.466	3.575	1.429
P value		0.397	0.410	0.226	0.059	0.232

Table 4. Baseline data and comparison of virological response rates and HBeAg serological conversion after the various treatment regimens

Parameters	Combined therapy	Entecavir	Telbivudine	Test Value	p value
	14	87	78		
Dyslipidemia (n, %)	5(35.7)	32(36.8)	31(39.7)	0.185	0.911
Male (n, %)	12(85.7)	73(83.9)	58(74.4)	2.640	0.267
Age (year)	46.3±11.7	39.±10.1	40.4±13.8	2.007	0.138
BMI (kg/m ²)	23.9±4.8	23.4±2.8	23.4±2.5	0.234	0.792
WBC (×10 ⁹ /L)	5.6±1.7	5.8±1.8	6.0±1.8	0.487	0.615
NE%	0.6±0.1	0.6±0.1	0.6±0.0	0.330	0.720
NE (×10 ⁹ /L)	3.4±1.4	3.3±1.4	3.5±1.4	0.230	0.795
RBC (×10 ¹² /L)	4.8±0.4	4.8±0.5	4.8±0.6	0.248	0.780
HB (g/L)	142.1±16.3	146.1±13.6	147.5±16.7	0.781	0.460
RDW (%)	13.8±2.1	13.6±3.1	13.0±0.9	1.757	0.176
PLT (×10 ⁹ /L)	221.6±97.1	216.2±68.3	226.3±62.6	0.444	0.642
PT (s)	14.0±1.8	13.4±0.9	13.4±1.0	2.418	0.092
PTA (%)	89.1±22.2	93.1±12.1	92.6±9.6	0.637	0.530
INR	1.1±0.3	1.0±0.1	1.0±0.1	3.547	0.031
F (g/L)	3.2±1.15	3.1±0.8	3.0±0.8	0.373	0.689
APTT (s)	37.5±6.4	37.3±4.2	36.6±5.1	0.498	0.609
APTTR	1.1±0.3	1.0±0.1	1.0±0.1	1.309	0.273
TT (s)	16.8±1.8	17.2±1.4	17.1±1.4	0.477	0.621
TTR	1.0±0.2	1.0±0.1	1.0±0.1	0.059	0.943
TB (umol/L)	58.6±131.3	16.2±15.6	15.1±12.8	1.530	0.465
DBIL (umol/L)	46.1±113.55	7.9±11.8	6.9±11.0	0.841	0.657
TP (g/L)	70.9±8.2	74.6±6.63	74.7±5.9	2.263	0.107
A (g/L)	42.7±7.1	44.3±5.6	44.4±4.9	0.621	0.539
ALT (U/L)	247.4±205.0	346.9±287.6	295.8±193.0	1.509	0.224
AST (U/L)	228.6±130.2	248.1±192.7	221.9±162.4	0.467	0.627
ALP (U/L)	81.4±26.6	88.3±21.8	85.0±23.5	0.805	0.449

R-GT (U/L)	56.6±37.9	78.8±56.6	71.4±37.4	1.492	0.228
FBG (mmol/L)	6.2±2.4	5.4±1.4	5.3±1.3	2.699	0.070
BUN (mmol/L)	4.4±1.5	4.7±1.3	4.6±1.1	0.358	0.699
CR (mmol/L)	62.4±15.9	69.2±11.2	68.3±14.6	1.629	0.199
UA (umol/L)	330.7±143.1	364.4±98.5	377.8±96.2	1.358	0.260
TC (mmol/L)	4.0±1.4	4.6±1.1	4.6±1.2	1.826	0.164
TG (mmol/L)	1.5±0.7	1.5±0.7	1.5±0.8	0.215	0.807
HDL-C (mmol/L)	0.9±0.3	1.1±0.3	1.1±0.3	4.091	0.018*
LDL-C (mmol/L)	2.3±1.1	2.7±0.9	2.8±1.0	1.759	0.175
HBsAg(S/CO)	8269.4±13647.8	5988.1±9224.3	5921.1±7409.6	0.434	0.649
HBeAg(S/CO)	944.3±549.4	798.9±455.3	832.3±573.9	0.491	0.613
HBVDNA Log ₁₀ IU/ml	7.9±0.8	7.5±1.2	7.5±1.1	0.625	0.537

Table 4. Baseline data and comparison of virological response rates and HBeAg serological conversion after the various treatment regimens (continued)

Parameters	Combined therapy	Entecavir	Telbivudine	Test Value	p value
	14	87	78		
The first year					
Virological Response	9(64.3)	59(67.8)	52(66.7)	0.076	0.963
HBeAg Serological Conversion	2(14.3)	13(14.9)	5(6.4)	3.147	0.207
The second year					
Virological Response	11(78.6)	63(72.4)	56(71.8)	0.276	0.871
HBeAg Serological Conversion	2(14.3)	13(14.9)	12(15.4)	0.014	0.993
The third year					
Virological Response	11(78.6)	72(82.8)	62(79.5)	0.343	0.843
HBeAg Serological Conversion	2(14.3)	15(17.2)	15(19.2)	0.243	0.886
The fourth year					
Virological Response	11(78.6)	78(89.7)	71(91)	1.943	0.379
HBeAg Serological Conversion	3(21.4)	22(25.3)	27(34.6)	2.152	0.341
The fifth year					
Virological Response	13(92.9)	82(94.3)	72(92.3)	0.252	0.882
HBeAg Serological Conversion	4(28.6)	29(33.3)	34(43.6)	2.343	0.310

Note: *variance analysis or nonparametric test in different treatment regimens $P < 0.05$.

Table 5. Single-factor logistic analysis

Baseline data	R value	OR (95% CI)
group	0.041*	1.965(1.026-3.761)
Male (n, %)	0.036*	2.212(1.005-4.639)
Age (years)	0.079	0.977(0.952-1.003)
Combined therapy (n, %)	0.177	0.647(0.344-1.271)
BMI (kg/m ²)	0.272	0.937(0.834-1.052)
WBC (×10 ⁹ /L)	0.352	0.919(0.770-1.098)
NE%	0.285	0.189(0.009-3.999)
NE (×10 ⁹ /L)	0.157	0.846(0.671-1.067)
RBC (×10 ¹² /L)	0.671	0.886(0.508-1.547)
HB (g/L)	0.603	1.005(0.985-1.026)
RDW (%)	0.240	0.837(0.622-1.126)
PLT (×10 ⁹ /L)	0.955	1.000(0.955-1.004)
PT (s)	0.065	1.362(0.981-1.890)
PTA (%)	0.004*	0.959(0.932-0.987)
INR	0.732	1.505(0.145-15.615)
F (g/L)	0.643	0.918(0.638-1.321)
APTT (s)	0.546	1.020(0.957-1.086)
APTTR	0.216	3.879(0.452-33.267)
TT (s)	0.648	1.051(0.848-1.303)
TTR	0.694	1.925(0.074-50.085)
TB (umol/L)	0.873	0.999(0.991-1.007)
DBIL (umol/L)	0.891	0.999(0.990-1.009)
TP (g/L)	0.450	0.982(0.937-1.029)
A (g/L)	0.370	0.975(0.920-1.031)
ALT (U/L)	0.000*	1.003(1.002-1.003)
AST (U/L)	0.000*	1.004(1.002-1.006)
ALP (U/L)	0.507	1.004(0.991-1.018)

r-GT (U/L)	0.135	1.005(0.998-1.011)
FBG (mmol/L)	0.896	0.986(0.801-1.214)
BUN (mmol/L)	0.441	0.904(0.700-1.168)
CR (mmol/L)	0.014*	0.970(0.946-0.994)
UA (umol/L)	0.635	1.001(0.998-1.004)
TC (mmol/L)	0.088	0.790(0.602-1.036)
TG (mmol/L)	0.250	0.780(0.511-1.191)
HDL-C(mmol/L)	0.769	1.161(0.428-3.153)
LDL-C (mmol/L)	0.022*	0.668(0.473-0.944)
HBsAg S/CO	0.979	1.000(1.000-1.000)
HBeAg S/CO	0.945	1.000(0.999-1.001)
HBV DNA Log ₁₀ IU/ml	0.061	0.774(0.592-1.012)

Note: *single-factor Logistic regression P<0.05.