

Original Research Article

Entecavir/peginterferon alfa-2a combination in the treatment of two genotypes of chronic hepatitis B patients with lamivudine resistance

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Abstract

Purpose: To investigate the efficacy of entecavir plus peginterferon alfa-2a in the treatment of chronic hepatitis B (CHB) patients with different hepatitis B virus (HBV) genotypes resistant to lamivudine (LAM).

Methods: 119 LAM-resistant CHB patients treated in Baoshan People's Hospital from May 2018 to May 2020 were selected. All patients received entecavir and peginterferon alfa-2a for 24 months and were scheduled for regular outpatient review and telephone follow-up. Polymerase chain reaction (PCR) was conducted to determine the HBV genotype and HBV-DNA clearance. Alanine aminotransferase (ALT) normalization rate, HBV-DNA clearance rates, and hepatitis B e-antigen (HBeAg) seroconversion rate were determined in CHB patients with different genotypes. Quality of life for all patients was assessed using SF-36 Scale.

Results: Five out of 119 patients were lost during follow-up, with a follow-up rate of 95.80 %. Two HBV genotypes were identified, of which 42 (36.8 %) were type B and 72 (63.2 %) type C. At the 6th and 12th month of follow-up, the HBV-DNA clearance rate, ALT normalization rate, and HBeAg seroconversion rate were significantly higher in CHB patients with genotype B than in patients with genotype C ($p < 0.05$). There were no significant differences between the three rates in the two groups at 18th and 24th month of follow-up ($p > 0.05$). The quality of life (QOL) of the patients differed between the two groups ($p < 0.05$).

Conclusion: Entecavir plus peginterferon alfa-2a are effective in treating LAM-resistant CHB patients with different genotypes. Genotype B CHB patients are more suitable for this combination protocol.

Keywords: Peginterferon alfa-2a, Entecavir, Lamivudine resistance, HBV genotypes, virological response

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INTRODUCTION

Restorative dentistry is a very crucial part of clinical dentistry, which mainly Chronic hepatitis

B is an inflammatory lesion of the liver, which is caused by HBV infection in humans, and some of the infections in patients gradually transform into cirrhosis or even liver cancer as their condition

worsens, affecting their safety and quality of life [1,2]. Since the introduction of the HBV vaccine, the prevalence of HBV has declined significantly, but it remains one of the most serious infectious diseases in the world [3]. Lamivudine belongs to the group of nucleotide drugs, which mainly act on HBV reverse transcriptase and DNA polymerase, thereby reducing HBV proliferation [4]. However, the LAM-associated resistance gene barrier is relatively low and HBV is more prone to drug-resistant mutations, which can produce a cumulative incidence of up to 18 % [5]. Therefore, the clinical focus of treatment for CHB should be on the development of a comprehensive antiviral regimen for LAM-resistant chronic HBV-infected patients [6].

It has been suggested that a combination regimen of pegylated interferon α -2a and entecavir should be used in the treatment of patients with LAM-resistant chronic hepatitis B. On the one hand, it aids the inhibition of HBV self-replication, and on the other hand, compared with entecavir alone, pegylated interferon α -2a produces both immunomodulatory factors as well as antiviral proteins, which perform immunomodulatory as well as antiviral effects [7,8]. Other studies have indicated that the HBV genotype of CHB patients is closely related to both HBV resistance mutations and the efficacy of antiviral therapy [9].

The combination of entecavir and peginterferon alfa-2a was used to treat LAM-resistant CHB patients, and the clinical efficacy and quality of life improvement were assessed through long-term follow-up to investigate the advantages and disadvantages of this treatment regimen in terms of virological and biological response, so as to select a more effective drug regimen for CHB patients with different HBV genotypes.

METHODS

Study population and ethical consideration

One hundred and nineteen CHB patients with LAM resistance who attended the Baoshan People's Hospital from May 2018 to May 2020 were selected. The study was approved by the Ethics Committee of Baoshan People's Hospital (approval no. 20180022) and followed the guidelines of the World Medical Association Declaration of Helsinki [10].

Inclusion criteria

Patients with an age range from 20 to 70 years old, positive serum hepatitis B surface antigen, diagnosed as CHB patients according to the

Chinese guidelines for the prevention and treatment of chronic hepatitis B (updated 2015 version) [11] and were on a combination regimen of pegylated interferon alpha-2a and entecavir applied to antiviral therapy after the development of LAM resistance were included in the study. (Patient LAM resistance criteria: elevated HBV-DNA quantification $> 1 \log \text{ IU/mL}$ in more than 2 consecutive serum tests compared to the lowest level after treatment) [12]. All patients signed the consent form prior to inclusion in the study.

Exclusion criteria

These included patients with renal insufficiency with creatinine clearance below 60 mL/min and patients taking other nucleoside antiviral drugs.

Treatments

All patients received combination antiviral therapy with entecavir and peginterferon alfa-2a for at least 2 years - entecavir tablets (Suzhou Dongrui Pharmaceutical Co. Ltd. State Drug Administration H20153021): 1.0 mg orally, once per day; peginterferon alfa-2a (Pegylated, Shanghai Roche Pharmaceutical Co. Ltd): 180 mg subcutaneously, once a week, for 2 years.

Patients' follow-up

All patients were followed up by regular outpatient and telephone visits at months 6, 8, 12, 18, and 24 to ensure adherence. Follow-up visits included monthly checks of HBeAg and HBV-DNA and liver function.

Evaluation of parameters/outcomes

Levels of HBeAg were determined using a MultiSkan enzyme marker (LABSYSTEMS Inc.) in the CHB patients. The genotype of HBV was determined through PCR using the HBV Genotyping Test Kit (Alcon Biotechnology Ltd). ABI 7500 real-time fluorescence quantitative PCR instrument (Thermo Fisher Scientific Inc.) and PCR kits (Tiangen Biochemical Technology (Beijing) Co., Ltd.) were conducted to determine serum HBV-DNA levels in CHB patients. A fluorometric quantification method was run to identify mutations in CHB patients' DNA polymerase Tyrosine-methionine-aspartate-aspartate (YMDD) gene.

Liver function indicators

Colorimetric methods were used to determine serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB), and total bilirubin (TBIL) levels in CHB patients

by conducting ADVIA 2400 fully automatic biochemical analyzer (Siemens Healthineers Inc.). Coagulation method was used to determine the prothrombin time (PT) of patients. The virological response and biochemical response of each patient at the 6th, 12th, 18th, and 24th months of follow-up were determined by Eqs 1 - 3.

$$\text{HBV-DNA clearance rate} = \frac{\{\text{negHBV-DNA}/N\}100}{\dots\dots\dots} \quad (1)$$

$$\text{ALT normalization rate} = \frac{(\text{nALT}/N)100}{\dots\dots\dots} \quad (2)$$

$$\text{HBeAg seroconversion rate} = \frac{(\text{nHBeAg}/N)100}{\dots\dots\dots} \quad (3)$$

where HBV - DNA clearance (defined as HBV - DNA level < 2log IU/mL), negHBV is the number of patients with negative HBV, nALT is the number of patients with ALT normalization (defined as ALT level < 40 U/L), nHBeAg is the number of patients with HBeAg seroconversion (HBeAg is negative and anti-HBe is positive) [13], and N is the total number of patients.

Short-Form 36(SF-36) Health Survey Scale

The SF-36 Scale was performed to assess the quality of life in both groups and physical functioning (PF), social functioning (SF), role limitations due to physical health problems (RP), role limitations due to personal or emotional functioning (RE), bodily pain (BP), mental health (MH), vitality (V) and general health (GH) were included, with scores ranging from 0 to 100 [14].

Statistical analysis

Statistical Package for Social Sciences (SPSS) 19.0 was used for data analysis. All the collected data are expressed as mean \pm SD. A *t*-test was performed for analysis of differences in the data, while chi-square test was applied for comparison between the count data.

The Kaplan-Meier method was used to compare the ALT normalization rate, cumulative HBV-DNA clearance rate, and HBeAg seroconversion rate among patients with different hepatitis B virus genotypes. Differences were considered significant when $p < 0.05$.

RESULTS

Follow-up results and genotype distribution

A total of 2 genotypes B and 3 genotypes C were lost from the 119 CHB patients initially included,

resulting in a follow-up rate of 95.80 %. Two HBV genotypes were identified in the remaining 114 patients, including 42 patients (36.8 %) with HBV genotype B and 72 patients (63.2 %) with HBV genotype C.

General information on patients with two HBV genotypes

There is no significant differences between patients with two HBV genotypes in terms of gender, age, the proportion of HBeAg positive, HBV-DNA level, YMDD mutation type, and levels of liver function ($P > 0.05$). As shown in Table 1.

HBV-DNA clearance rates in patients with two HBV genotypes

At months 6, 12, 18, and 24 of follow-up, HBV-DNA clearance rates for the 114 CHB patients were 42.86 % (37 cases), 57.89 % (66 cases), 78.07 % (89 cases), and 92.11 % (105 cases). The clearance rates of HBV-DNA were 42.86 % (18 cases), 69.05 % (29 cases), 80.95 % (34 cases), and 95.24 % (40 cases) in patients with genotype B, while clearance rates were 26.39 % (19 cases), 51.39 % (37 cases), 76.38 % (55 cases), and 90.28 % (65 cases) in patients with genotype C. At months 6 and 12, the HBV-DNA clearance rate was significantly higher in patients with CHB type B than in patients with CHB type C, ($p < 0.05$), while there was no significant difference in the HBV-DNA clearance rate between patients with both HBV genotypes ($P > 0.05$) at months 18 and 24, as shown in Table 2.

ALT normalization rate in patients with two HBV genotypes

At the 6th, 12th, 18th, and 24th month of follow-up, ALT normalization rates of 114 patients with CHB were 28.95 % (33 cases), 57.02 % (65 cases), 73.68 % (84 cases) and 85.09 % (97 cases). ALT normalization rates in HBV genotype B patients were 38.01 % (16 cases), 66.67 % (28 cases), 78.57 % (33 cases), and 90.48 % (38 cases), while ALT normalization rates for HBV genotype C patients were 22.61 % (17 cases), 51.39 % (37 cases), 70.83 % (51 cases) and 81.94 % (59 cases). At months 6 and 12, the ALT normalization rate was significantly higher in CHB patients with type B than in patients with type C, with a significant difference ($p < 0.05$); at months 18 and 24, there was no significant difference between the two groups ($p > 0.05$), as shown in Table 3.

Table 1: General information on patients with two HBV genotypes

Genotype	Age	Male (case)	HBV-DNA (log IU/mL)	YMDD mutation, case				HBeAg positive (case)	AST (U/L)	ALT (U/L)	TBIL (μmol/L)	ALB (mmol/L)	PT (s)
				YM DD	YI DD	YV DD	YIDD+ YVDD						
Type B n=42	49.6±4.0	35	6.5±0.8	1	19	21	1	40	105.4±28.8	95.8±24.6	56.9±10.3	30.4±1.3	16.6±2.0
Type C n=72	49.3±4.5	45	6.9±1.0	1	38	31	2	69	108.9±25.4	102.9±29.2	52.9±11.4	31.2±1.2	17.0±2.1
<i>t</i>	0.02	0.174	0.397			0.733		0.056	0.824	1.032	0.811	0.815	0.819
<i>P</i> -value	0.88	0.663	0.850			0.856		0.823	0.392	0.277	0.395	0.426	0.395

Table 2: HBV-DNA clearance rates in patients with two HBV genotypes

Genotype	N	6 months	12 months	18 months	24 months
Type B	42	18 (42.86%)	29 (69.05%)	34 (80.95%)	40 (95.24%)
Type C	72	19 (26.39%)	37 (51.39%)	55 (76.38%)	65 (90.28%)
χ^2		4.581	4.680	1.960	2.468
<i>P</i> -value		0.032	0.031	0.162	0.116

Table 3: ALT normalization rate in patients with two HBV genotypes

Genotype	N	6 months	12 months	18 months	24 months
Type B	42	16 (38.01%)	28 (66.67%)	33 (78.57%)	38 (90.48%)
Type C	72	17 (22.61%)	37 (51.39%)	51 (70.83%)	59 (81.94%)
χ^2		4.070	3.912	2.399	3.021
<i>P</i> -value		0.044	0.048	0.121	0.082

HBeAg seroconversion rates in patients with two HBV genotypes

At the 6th, 12th, 18th, and 24th month of follow-up, HBeAg seroconversion rates in the 114 CHB patients were 10.53 % (12 cases), 20.18 % (23 cases), 28.07 % (32 cases) and 33.33 % (38 cases). The HBeAg seroconversion rates were 16.67 % (7 cases), 28.57 % (12 cases), 33.33 % (14 cases), and 38.10 % (16 cases) in CHB patients with genotype B, while those were 6.94 % (5 cases), 15.28 % (11 cases), 25.00 % (18 cases) and 30.56 % (22 cases) in CHB patients with genotype C in all follow-up periods. At months 6 and 12, the HBeAg seroconversion rate was significantly higher in CHB patients with genotype B than in patients with genotype C, with significant differences ($p < 0.05$). At months 18 and 24, there was no significant difference in HBeAg seroconversion rates between the two groups ($p > 0.05$), as stated in Table 4.

Quality of life of patients with two HBV genotypes

After treatment with entecavir in combination with peginterferon alfa-2a, the values of PF, RP, MH, RE, and total scores were significantly higher in both groups of CHB patients than during pre-treatment, while the values of SF, BP, and V were significantly lower, with significant differences between the same groups before and after treatment ($p < 0.05$). The QOL of CHB patients with genotype B was better than that of patients with genotype C, and the difference in

QOL was significant between the two groups ($p < 0.05$, Table 5).

DISCUSSION

With the development and improvement of pharmaceutical therapy options for CHB, the process of CHB can be slowed down by blocking HBV replication [15]. However, drug resistance in some CHB patients is still difficult to overcome. Lamivudine is the first nucleotide-based, anti-HBV drug approved for marketing in China, LAM significantly reduces HBV-DNA quantification in CHB patients, enhances the seroconversion rate of HBeAg, delays liver tissues necrosis and reverses liver tissue fibrosis [16]. However, LAM resistance is easy to develop in CHB patients, in the first 5 years when LAM was selected as the main drug for CHB treatment, the incidence of drug resistance increased year by year. Mutations in the DNA polymerase YMDD gene have been reported to be associated with the development of LAM resistance. [5]. Among the 114 LAM-resistant CHB patients, the proportion of YMDD gene mutations was high (98.2 %), and there was 1 patient with no YMDD gene mutation in both genotype B and genotype C patients.

Peginterferon α -2a is an anti-HBV immunomodulator, but it is poorly tolerated only by injection and is expensive, all of these limits its widespread use [17]. Entecavir, as one of the current anti-HBV therapeutic drugs, significantly inhibits HBV replication, reduces the occurrence of liver inflammation, decreases the activity of stellate cells and the formation of collagen fibers

Table 4: HBeAg seroconversion rates in patients with two HBV genotypes

Genotype	N	6 months	12 months	18 months	24 months
Type B	42	7(16.67%)	12(28.57%)	14 (33.33%)	16 (38.10%)
Type C	72	5 (6.94%)	11 (15.28%)	18 (25.00%)	22 (30.56%)
χ^2		4.032	4.252	2.482	2.272
P-value		0.047	0.039	0.115	0.132

Table 5: Quality of life in patients with two HBV genotypes

Genotype	Observation period	PF /score	RP score	MH score	SF score	BP score
Type B (n=42)	Pre-treatment	11.25±1.25	3.44±0.25	2.46±0.64	5.23±0.54	5.28±0.42
	Post-treatment	24.44±4.49*	5.50±1.46*	4.28±1.33*	3.34±1.76*	2.09±0.90*
Type C (n=72)	Pre-treatment	10.04±1.15	3.42±0.21	2.45±0.92	5.22±0.51	5.35±0.15
	Post-treatment	29.35±2.92*▲	7.35±0.92*▲	5.62±0.78*▲	2.14±0.63*▲	1.37±0.65*▲
Genotype	Observation time	V score	RE score	GH score	Total / score	
Type B (n=42)	Pre-treatment	5.49±0.25	29.46±4.27	20.25±1.34	96.18±5.15	
	Post-treatment	2.18±1.17*	36.57±4.31*	20.32±1.98	102.36±6.65*	
Type C (n=72)	Pre-treatment	5.41±0.51	30.36±4.25	20.08±1.41	96.45±5.42	
	Post-treatment	1.33±0.54*▲	37.83±4.44*▲	20.07±1.79	109.16±5.66*▲	

* $P < 0.05$, Compared with the same group before treatment; ▲ $P < 0.05$, there were significant differences between the two genotypes of CHB patients after treatment

in liver tissue, and slows down the process of liver fibrosis [18]. Therefore, compared with other antiviral drugs, entecavir has a more rapid viral suppressive effect and a higher safety profile, especially in patients with liver failure, and it effectively prolongs the survival of patients. Peginterferon alfa-2a and entecavir are both CHB therapeutic drugs, but their mechanisms of action are different. Therefore, the combination of them could theoretically be more effective in inhibiting HBV replication and reducing both drug resistance and liver damage [8].

Currently, at least 10 HBV genotypes (A~X) have been identified worldwide, with a more distinct geographical distribution, and with type B (southern region) and type C (northern region) predominant in China. A study by Zhang *et al* [6] demonstrated that there was no significant difference in the rate of drug-resistant mutations among the three HBV genotypes, B, C, and D. Moreover, the development of drug resistance was accompanied by mutations in drug-resistant genes, and such changes may increase the chances of CHB transforming into cirrhosis or liver cancer. Another study revealed that there was no significant difference between patients with hepatitis B and type C in terms of ALT recurrence rate, as well as HBeAg seroconversion rate under the same treatment regimen. There was also no significant difference in the HBV-DNA clearance rate between patients with type B and type C, except after 6 months of follow-up [19]. The genotype analysis of the patients showed that the genotype of the 114 hepatitis B virus patients was predominantly genotype C, accounting for 63.2 % of the total patients. The results of the treatment regimen with peginterferon alfa-2a in combination with entecavir in patients with both hepatitis B virus genotypes have not been conclusive.

However, in this study, it was found that at months 6 and 12, the HBV-DNA clearance rate, ALT regression rates, and HBeAg seroconversion rate were significantly better in patients with genotype B CHB than in patients with genotype C CHB. This is a significant difference from previous studies. In addition, the QOL of all patients was also included in the followed up, and results demonstrated that the QOL of patients treated with peginterferon alfa-2a in combination with entecavir improved significantly, with patients with genotype B CHB showing significantly better improvement than those with genotype C CHB.

This further suggests that genotype B is more sensitive to the above combination regimen and has a better viral and biochemical response than

genotype C. However, the mechanism is not fully yet understood, and further experiments are needed to verify this. Possible reasons for this are that genotype C has a higher frequency of mutations in the underlying core promoter A1762T/G1764A than genotype B, in patients with chronic hepatitis B. Patients with genotype C has a higher lifetime risk of developing cirrhosis and HCC than genotype B.

Limitations of the study

Although the follow-up period of this study was long, the sample size was not large enough, and the conclusions drawn may not be generalizable.

CONCLUSION

The combination of entecavir and peginterferon alfa-2a is effective in treating CHB patients with LAM-resistant. The viral and biochemical responses and the QOL scores of patients with genotype B are better than those of CHB patients with genotype C. These findings need to be validated via further experiments *in vivo* and *in vitro*.

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Ethical approval

None provided.

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Xiaoyun Peng and Mingying Xiao conceived and designed the study. Xiaoyun Peng and Longgui

Chen collected and analyzed data, while Xiaoyun Peng wrote the manuscript which was approved by all authors.

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REFERENCES

1. Tsai KN, Kuo CF, Ou JJ. Mechanisms of Hepatitis B virus persistence. *Trends Microbiol* 2018; 26(1): 33-42.
2. Shih C, Yang CC, Chojjilsuren G, Chang CH, Liou AT. Hepatitis B virus. *Trends Microbiol* 2018; 26(4): 386-387.
3. Mohanty P, Jena P, Patnaik L. Vaccination against Hepatitis B: A scoping review. *Asian Pac J Cancer Prev* 2020; 21(12): 3453-3459.
4. Haché C, Villeneuve JP. Lamivudine treatment in patients with chronic hepatitis B and cirrhosis. *Expert Opin Pharmacother* 2006; 7(13): 1835-1843.
5. Liu X, Schinazi RF. Hepatitis B virus resistance to lamivudine and its clinical implications. *Antivir Chem Chemother* 2002; 13(3): 143-155.
6. Zhang J, Wang Y, Peng Y, Qin C, Liu Y, Li J, Jiang J, Zhou Y, Chang J, Wang Q. Novel fluoronucleoside analog NCC inhibits lamivudine-resistant hepatitis B virus in a hepatocyte model. *Braz J Infect Dis* 2018; 22(6): 477-486.
7. Chen S, Zhou J, Wu X, Meng T, Wang B, Liu H, Wang T, Zhao X, Kong Y, Wu S, et al. Comparison of fibrosis regression of entecavir alone or combined with pegylated interferon alpha2a in patients with chronic hepatitis B. *Hepato Int* 2021; 15(3): 611-620.
8. Hagiwara S, Nishida N, Watanabe T, Ida H, Sakurai T, Ueshima K, Takita M, Komeda Y, Nishijima N, Osaki Y, et al. Sustained antiviral effects and clearance of hepatitis surface antigen after combination therapy with entecavir and pegylated interferon in chronic hepatitis B. *Antivir Ther* 2018; 23(6): 513-521.
9. Archampong TN, Boyce CL, Lartey M, Sagoe KW, Obo-Akwa A, Kenu E, Blackard JT, Kwara A. HBV genotypes and drug resistance mutations in antiretroviral treatment-naïve and treatment-experienced HBV-HIV-coinfected patients. *Antivir Ther* 2017; 22(1): 13-20.
10. Ballantyne A, Eriksson S. Research ethics revised: The new CIOMS guidelines and the World Medical Association Declaration of Helsinki in context. *Bioethics* 2019; 33(3): 310-311.
11. Wang GQ, Wang FS, Cheng J, Ren H, Zhuang H, Sun J, Li LJ, Li j, Meng QH, Zhao JM, et al. Guidelines for the prevention and treatment of chronic hepatitis B (updated 2015). *Chin J Hepatol* 2015; 23(12): 888-905.
12. Li MH, Zhang L, Qu XJ, Lu Y, Shen G, Li ZZ, Wu SL, Liu RY, Chang M, Hu LP, et al. The predictive value of baseline HBsAg level and early response for HBsAg loss in patients with HBeAg-positive chronic hepatitis B during peginterferon alfa-2a treatment. *Biomed Environ Sci* 2017; 30(3): 177-184.
13. Xie YD, Ma H, Feng B, Wei L. Efficacy of real-world entecavir therapy in treatment-naïve chronic hepatitis B patients. *Chin Med J (Engl)* 2017; 130(18): 2190-2197.
14. Doosti-Irani A, Nedjat S, Nedjat S, Cheraghi P, Cheraghi Z. Quality of life in Iranian elderly population using the SF-36 questionnaire: systematic review and meta-analysis. *East Mediterr Health J* 2019; 24(11): 1088-1097.
15. Wu W, Jiang C, Cheng C, Sun Y, Luo N, Ge J. Combined effects of tenofovir and interferon α 5:1b on viral load and levels of peripheral regulatory T cells in chronic hepatitis B subjects. *Trop J Pharm Res* 2019; 18(4): 863-868.
16. Lapinski TW. The concentration of Fas in the serum and liver tissue in viral chronic hepatitis B patients treated with lamivudine. *Hepatogastroenterol* 2005; 52(62): 575-579.
17. Hu JH, Chang ML, Huang TJ, Yeh CT, Chiu WN, Chiang MS, Chen MY. Comparison of compliance and efficacy of pegylated interferon α -2a and α -2b in adults with chronic hepatitis C. *J Interferon Cytokine Res* 2019; 39(4): 205-213.
18. Choi WM, Choi J, Lim YS. Effects of tenofovir vs entecavir on the risk of hepatocellular carcinoma in patients with chronic HBV infection: A systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2021; 19(2):246-258.e9.
19. Caifang C, Jingjing F, Hao W. Therapeutic efficacy of lamivudine combined with adefovir dipivoxil in the treatment of lamivudine-resistant chronic Hepatitis B patients and its relationship with HBV genotype. *China Pharm* 2017; 28(29): 4037-4041.