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Clinical efficacies of initial combined application of lamivudine and adefovir dipivoxil in treating decompensation stage of hepatitis-B caused cirrhosis.

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Abstract

This study aims to investigate the clinical efficacies of initial combined application of Lamivudine (LAM) and Adefovir Dipivoxil (ADE) in treating the Decompensation Stage of Hepatitis B-caused Cirrhosis (DS-HBC). 200 DS-HBC patients treated were selected and randomly divided into the Observation group (OBS) and the Control group (CON): The observation group was administrated the initial combined therapy of LAM and ADE, and the control group was co-administrated LAM after ADE-resistance appeared. Such indexes as HBeAg/HBeAb seroconversion, HBV-DNA outcome, Child-Pugh score, and liver functions between the two groups after 6 and 12-month treatment were then compared. The HBeAg/HBeAb seroconversion in OBS was higher than CON (6 month: 37% *vs.* 19%, 12 month: 69% *vs.* 43%), the HBV DNA negative-conversion rate was also higher (6 month: 38% *vs.* 21%, 12 month: 88% *vs.* 54%), the Child-Pugh score was significantly lower than CON (6 month: 8.9 ± 0.5 *vs.* 9.2 ± 0.5; 12 month: 7.5 ± 0.4 *vs.* 8.7 ± 0.9), and the liver functions were better than CON. The differences in the above results between the two groups were statistically significant (P<0.05). The clinical efficacies of initial combined application of LAM and ADE in treating DS-HBC were better those of second-line combined therapy, so it was worthy of promotion.

Keywords: Lamivudine, Adefovir dipivoxil, Liver cirrhosis.

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Introduction

Nowadays, it is estimated that chronic Hepatitis B Virus (cHBV) infection affects 370 million people worldwide [1]. The current goal in treating cHBV infection is to block the progression of HBV-related liver injury and inflammation to end-stage liver diseases, including cirrhosis and hepatocellular carcinoma because cHBV infection is still unable to be eliminated [2]. Current therapies remain limited to either Pegylated Interferon-α (Peg-IFN-α), or one of the five approved Nucleoside Analog (NA) treatments [3], including lamivudine, adefovir, telbivudine, entecavir, and tenofovir, which have been approved as nucleoside/nucleotide inhibitors of the HBV polymerase. The mechanisms are targeting at DNA elongation and impairing protein priming, thus delaying the progression of cHBV [4]. So, mutation conferred nucleoside/nucleotide analog resistance include the combinations of rtL180M/rtM204 (I/V) (for lamivudine, entecavir, telbivudine and clevudine) and rtA181V/rtN236T (for adefovir and tenofovir) [5].

Nowadays, 25-35% of infected individuals eventually die due to the complications of liver cirrhosis and Hepatocellular Carcinoma (HCC) induced by HBV [6]. A number of studies have shown that HBV DNA viral load was a key indicator that could effectively predict the occurrence, development, and outcomes of cirrhosis. Although viral suppression could be achieved in the majority of patients, HBsAg loss is achieved in only 10% of patients with both classes of drugs after a 5 year follow-up [7]. But virus relapse always happens; one study collected 103 cases, and virus relapse occurred in 26 (57.8%) HBeAg-positive patients and in 37 (54.4%) HBeAg-negative patients within 1 year after NA treatment [8]. Until now, although many new antiviral therapies have been developed for the management of hepatitis B, they still could not offer the possibility of cure [9].

Even after achieving virological suppression on LAM therapy, the risk of emergent LAM resistance increases over time. Switching to entecavir resulted in a maintained virologic response and superior serologic responses *vs.* continued LAM therapy [10]. But due to the high price of the third-generation antiviral drug entecavir, the majority of patients are still unable to adhere to long-term medication.

One study had confirmed that to LAM-resistant cHBV patients, 5 year adefovir add-on rescue therapy made 92.1% of patients achieve favourable response [11]. We investigated the clinical efficacies of initial combined application of LAM and ADE in treating DS-HBC, and now reported below.

Materials and Methods

General information

200 DS-HBC patients treated in our hospital from 2009.6 to 2014.6 were selected and randomly divided into OBS and CON. The whole study was performed with all the patients' informed consent. Patients combined with vital organ dysfunctions such as heart, brain, or kidney, coagulation system impairment, or bleeding disorder were excluded. The 100 patients in OBS aged 24 to 67 years old, and the 100 patients in CON aged 21 to 69 years old. The two groups showed no significant difference in age, sex, or disease conditions (P>0.05), therefore, these two groups were comparable. The specific data were shown in Table 1. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the Second people's Hospital of Yibin (2014-0901). Written informed consent was obtained from all participants.

Grouping

All the patients were confirmed as DS-HBC on admission. According to the random number table method, the patients were randomly divided into OBS and CON. The 100 patients in OBS was applied the initial combined treatment of LAM (once per day, 100 mg/time, Manufacturer: GlaxoSmithKline) and ADE (once per day, 100 mg/time, starting 2 weeks after the administration of LAM, Manufacturer: GlaxoSmithKline (Tianjin) Co., Ltd.). The 100 patients in CON was firstly administrated ADE, and then applied the combined treatment of LAM and ADE when mutation occurred, and the dosage and the usage were the same as OBS.

Outcome indexes

The HBeAg/HBeAb seroconversion, HBV-DNA outcome, Child-Pugh score, and liver functions (AST, ALT, TBiL, and ALB) between the two groups after 6 and 12-month treatment were then compared.

Statistical analysis

SPSS 18.0 statistical software was used for the data analysis; the data were expressed as mean ± standard deviation ($\bar{x} \pm s$), the comparison of mean data used the t test, and the comparison of measurement data used the χ^2 test, with P<0.05 considered as statistically significant difference.

Results

Analysis and comparison of HBeAg/HBeAb seroconversion, HBV DNA negative-conversion rate, and child-Pugh score between the two groups

After 6 month combined therapy, HBeAg/HBeAb seroconversion in OBS and CON were 37% and 19%, respectively, showing significant difference (χ^2=8.0357, P=0.0046); HBV DNA negative-conversion rates in OBS and CON were 38% and 21%, respectively, showing significant difference (χ^2=6.9480, P=0.0084); the Child-Pugh score in OBS was lower than CON, showing significant difference (t=4.2426, P<0.0001). After 1 year combined therapy, HBeAg/HBeAb seroconversion and HBV DNA negative-conversion rate in OBS were higher than CON (P<0.05), but the Child-Pugh score was lower than CON (P<0.05). The specific data were shown in Table 2.

Analysis and comparison of liver functions between the two groups

After 6 month combined therapy, the liver function indicators (AST, ALT, TBiL, and ALB) in OBS were better than CON and closer to normal values (P<0.05); after 1 year combined therapy, the liver function indicators observation group (AST, ALT, TBiL, and ALB) in OBS were better than CON and much more close to normal values (P<0.05). The specific data were shown in Table 3.

Table 1. *Analysis and comparison of general clinical situations between the two groups.*

Item	OBS (n=100)	CON (n=100)	Stat	P
Age (years)	42.58 ± 12.38	41.75 ± 12.44	0.4729	0.6368
Gender (n (%))				
M	67 (67.00)	65 (65.00)	0.0891	0.7653
F	33 (33.00)	35 (35.00)		
HBeAg (n (%))				
Positive	45	47	0.0805	0.7766
Negative	55	53		
ALT (U/L)	147.45 ± 67.67	151.23 ± 53.33	0.4387	0.6613
Child-Pugh score (points)	9.78 ± 1.12	9.67 ± 1.22	0.6642	0.5073
HBV DNA (lg copies/ml)	5.44 ± 0.67	5.43 ± 0.25	0.1398	0.8889
TBil (umol/L)	72.12 ± 23.23	74.23 ± 24.34	0.6271	0.5313
Alb (g/L)	25.33 ± 2.12	24.98 ± 2.44	1.0828	0.2802

Discussion

As we know, one third of the world's population has been infected with HBV [12,13], and HBV infection is a major public health threat in the Asia-Pacific region [14,15]. In China, the HBsAg carrier rate was 9.75% in 1992 [16], and 7.18% in 2006 [17], which is significantly higher than that of the Western countries [18], and HBV-related diseases cause heavy financial burdens which is positively associated with disease severities [19]. HBV infection is the major cause of cirrhosis in China, and when the patients develop into the decompensation stage of cirrhosis later, the 5 year mortality could be as high as 70% to 85% [20]. It's a relatively long process to develop from cHBV infection to cirrhosis or liver

cancer, which could be as long as 15 years or more, so patients with cirrhosis normally have long-term history of viral infection, and there might exists many non-standard medications in their previous treatments [21].

At the same time, the complexity of anti-viral therapy in patients with cirrhosis is significantly higher than in patients with cHBV; a number of studies indicate that the antiviral therapy of LAM could delay the progression of cirrhosis, significantly improve the liver functions, correct the decompensation of the liver functions, and slow liver damages, thus improving and enhancing patients' liver functions, and thus improving the survival rate and survival period of patients [22]. However, long-term drug therapy would easily lead to YMDD mutation and drug-resistance, thus reducing the clinical treatment effects.

ADE is one analog of adenosine monophosphate nucleotide and could compete the viruses in binding with the substrate of deoxyadenosine triphosphate, thus inhibiting the activities of HBV DNA polymerase or reverse transcriptase and reducing its activities; it could also enter HBV DNA, block the elongation of the virus DNA chain, thus inhibiting the replication of the viruses. In addition, other studies also found that ADE had good inhibition against wild strains, as well as significant inhibition against LAM-resistant HBV viruses [23].

LAM could rapidly inhibit the virus; its rapid onset is its advantage, but its disadvantage is that it's prone to cause the viral mutation; ADE has slow effects, but it's not easy to cause the viral mutation [24]. Studies have found good results and recommended the combined therapy of LAM and ADE for DS-HBC patients. Our study showed that the HBeAg/HBeAb seroconversion rates in the patients with 6 month initial combined therapy of LAM and ADE and those applied the combined therapy of LAM and ADE after LAM-caused mutation occurred were 37% and 19%, respectively, and the HBV DNA negative-conversion rates were 38% and 21%, indicating the effects of initial LAM-ADE combination therapy were superior to the latter. The Child-Pugh score in OBS was also lower than CON. After 1 year combined therapy, the results of HBeAg/HBeAb seroconversion, HBV DNA negative-conversion rate, and Child-Pugh score in OBS were all superior to those in CON.

When patients enter DS-HBC, their liver functions would occur significant decreasing, and non-prompt treatment would lead to more rapid and severe liver function declining, which might further lead to liver failure [25]. Our study showed that the liver function indicators (AST, ALT, TBiL, and ALB) in OBS after 6 month and 1 year combination therapy were better than CON.

This study showed that the initial combined therapy of LAM and ADE could significantly increase patients' HBeAg/HBeAb seroconversion and HBV DNA negative-conversion rate, significantly reduce the Child-Pugh score, and effectively improve the liver functions.

In summary, the clinical efficacies of the initial combined therapy of LAM and ADE in treating DS-HBC were good, so this method was worthy of clinical promotion.

Table 2. *Analysis and comparison of HBeAg/HBeAb seroconversion, HBV DNA negative-conversion rate, and Child-Pugh score between the two groups.*

Item	Cases	HBeAg/HBeAb seroconversion (n (%))		HBV DNA negative-conversion rate (n (%))		Child-Pugh score (points)	
		6 month combined therapy	1 year combined therapy	6 month combined therapy	1 year combined therapy	6 month combined therapy	1 year combined therapy
OBS	100	37 (37.00)	69 (69.00)	38 (38.00)	88 (88.00)	8.9 ± 0.5	7.5 ± 0.4
CON	100	19 (19.00)	43 (43.00)	21 (21.00)	54 (54.00)	9.2 ± 0.5	8.7 ± 0.9
Stat		8.0357	13.7175	6.948	28.0719	4.2426	12.1842
P		0.0046	0.0002	0.0084	<0.0001	<0.0001	<0.0001

Table 3. *Analysis and comparison of liver functions between the two groups ($\bar{x} \pm s$).*

Item	Cases	AST (U/L)		ALT (U/L)		TBiL (umol/L)		ALB (g/L)	
		6 month combined therapy	1 year combined therapy	6 month combined therapy	1 year combined therapy	6 month combined therapy	1 year combined therapy	6 month combined therapy	1-year combined therapy
OBS	100	92.2 ± 19.5	56.3 ± 8.6	87.3 ± 23.4	51.3 ± 12.3	37.2 ± 12.3	30.2 ± 5.5	33.2 ± 2.3	35.5 ± 2.1
CON	100	112.2 ± 15.7	83.3 ± 16.4	164.3 ± 33.2	101.3 ± 32.3	55.3 ± 13.5	48.6 ± 8.6	30.2 ± 1.9	31.2 ± 2.4
t		7.9889	14.5803	18.9572	14.4665	9.9107	18.0245	10.056	13.4837
P		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Conflicts of Interest

All of the authors declare that they have no conflicts of interest regarding this paper.

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