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ORIGINAL ARTICLE

Nucleoside analogues improve the short-term and long-term prognosis of patients with hepatitis B virus-related acute-on-chronic liver failure

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Abstract Hepatitis B virus (HBV) infection is a major public health problem, and HBV-related acute-on-chronic liver failure (ACLF) has an extremely poor prognosis. There is no standard approach for managing ACLF. Nucleos(t)ide analogue has been proven effective in suppressing viral replication, improving histology and biochemical, and decreasing the inflammatory response in patients with chronic hepatitis B. This study was designed to evaluate the short-term and long-term efficacy of nucleoside analogue treatment of patients with HBV-related ACLF. One hundred and six consecutive subjects were recruited from 2,308 patients with elevated alanine aminotransferase activity. Forty-two patients were treated with 0.5 mg entecavir (ETV) daily (ETV group); 30 patients received 100 mg lamivudine (LAM) daily (LAM group); 34 patients did not take any nucleos(t)ide analogues (non-NAs group). All eligible patients were given standard medical treatment. All the patients were followed up until death or until October 2010. The HBV DNA levels and the short-term and long-term efficacy of the drugs were evaluated. After 3 weeks of nucleoside analogue treatment and/or supportive therapy, HBV DNA levels were decreased when compared with the baseline level in the ETV group (7.04 ± 1.58 $\log_{10}$ IU/mL vs. 4.03 ± 2.04 $\log_{10}$ IU/mL, $P = 0.001$), the LAM group (7.25 ± 0.89 $\log_{10}$ IU/mL vs. 4.33 ± 2.48 $\log_{10}$ IU/mL, $P = 0.01$), and the non-NAs group (5.73 ± 0.96 $\log_{10}$ IU/mL vs. 4.21 ± 1.47 $\log_{10}$ IU/mL, $P = 0.01$). The ETV and LAM groups showed a similar accumulative mortality in the first 3 months of treatment (33.3% vs. 40%, $\chi^2 = 0.568$, $P = 0.374$). The non-NAs group had a significantly high mortality, compared with the ETV group (64.7% vs. 33.3%, $\chi^2 = 7.163$, $P = 0.007$), the LAM group (64.7% vs. 40%, $\chi^2 = 3.906$, $P = 0.042$), and the nucleoside analogue group (ETV group + LAM group) (64.7% vs. 36.2%, $\chi^2 = 7.443$, $P = 0.006$). All the 56 patients survived were followed up to October 2010. The median follow-up period was 7.3 months. Recurrence was observed in a total of 6 patients (10.72%), of whom 4 patients (33.33%) were from the non-NAs group, 2 (11.11%) from the LAM group after cessation LAM therapy by patients himself, and 0 from the ETV group ($P = 0.003$). Nucleoside analogue may improve the short-term and long-term prognosis of patients with HBV-related ACLF.

Keywords Enticavir · Lamivudine · Hepatitis B virus · Acute-on-chronic liver failure

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Introduction

Hepatitis B virus (HBV) infection is a major public health problem. According to World Health Organization, approximately 400 million people worldwide are affected by chronic HBV infection and roughly one million people die annually from HBV-related diseases [1]. Chronic HBV infection causes a spectrum of diseases such as chronic hepatitis B, cirrhosis, hepatocellular carcinoma, and liver failure. HBV-related acute-on-chronic liver failure (ACLF)

is a clinical syndrome defined as acute hepatic insult with diagnosed or undiagnosed chronic liver disease [2]. The major liver functions, particularly synthetic function, detoxification, and metabolic regulation, are impaired to different degrees, probably resulting in life-threatening complications such as hepatic encephalopathy, hepatorenal syndrome, severe jaundice, ascites, and coagulopathy, which have a high mortality rate of 50–90%. Only a limited number of medical treatments are available for ACLF. Although liver transplantation is a life-saving treatment for ACLF, the difficulty in finding a suitable donor and the high cost hinder its extensive clinical use.

The precise mechanism underlying the liver injury caused by HBV-related ACLF and the factors contributing to the progression of liver failure remain unknown. Generally, virus factors, host factors, and their interaction determine the result of ACLF. HBV DNA replication is one of the key factors causing the progression from liver damage to liver failure. The HBV DNA level is closely associated with the risk of hepatocellular carcinoma development, and HBV DNA suppression significantly improves the prognosis of cirrhosis. Current clinical guidelines advocate oral antiviral treatment in decompensated cirrhosis and sustained HBV DNA suppression to reduce sequelae [1–5]. Four nucleotide/nucleoside analogues (NAs) (lamivudine, adefovir dipivoxil, enticavir, and telbivudine) have been used for the treatment of CHB. However, limited data are available from the Eastern and Western world on the use of antiviral treatment among patients with ACLF [6, 7]. Here, we report a single-center experience of the use of NAs in 106 patients with HBV-related ACLF. To the authors' knowledge, this is one of the biggest single-center experiences of the use of antiviral treatment to date.

Patients

A retrospective review was carried out of adult patients with HBV-related ACLF, who visited the First Affiliated Hospital of Xi'an JiaoTong University, China between January 2008 and May 2010. In China, most patients infected HBV during early childhood.

ACLF was diagnosed according to the diagnostic criteria recommended by the Asian Pacific Association for the Study of the Liver (APASL) [2], i.e., two insults to liver are operating simultaneously: one of them being ongoing and chronic and the other being acute. The inclusion criteria were defined as follows: (1) age 18–65 years; the presence of hepatitis B surface antigen in the serum for at least 6 months; HBV DNA level above 3 log10 IU/mL; (2) recent development of increasing jaundice (a total serum bilirubin concentration of above 85 μmol/L) and a decrease in plasma prothrombin activity (PTA) (<40%) or with an international standard ratio (INR) of above 1.5; (3) recent development of complications such as hepatic encephalopathy, or abrupt and obvious increase in ascites, or spontaneous bacterial peritonitis, or hepatorenal syndrome. The exclusion criteria included the following: (1) patients who suffered from hepatitis A, hepatitis C, hepatitis D, hepatitis E, Epstein–Barr virus, or other virus infections; (2) patients with drug-induced hepatitis, Wilson's disease, alcoholic liver disease, and autoimmune hepatitis.

The study protocol was in accordance with the ethical guidelines of the Declaration of Helsinki (1995) and was approved by the independent ethics committee at the First affiliated Hospital of Xi'an JiaoTong University, China.

Treatment schedule

A total of 2,308 patients were admitted to the Division of infectious diseases, the First affiliated Hospital of Xi'an JiaoTong University between July 2008 and June 2010. All the patients with elevated alanine aminotransferase (ALT) were detected; HBV marker and history were taken to diagnose chronic HBV infection. Of the 2,308 in-patients with hepatitis, 1,386 patients were diagnosed with chronic HBV infection; of the 1,386 patients, 168 were diagnosed with ACLF and met the inclusion criteria mentioned above; of the 168 patients, 21 were excluded according to the exclusion criteria. As a result, a total of 147 adult patients with ACLF were recruited for the study. Of the 147 patients, 42 were required to receive 0.5 mg entecavir (ETV) daily (ETV group), 30 were required to receive 100 mg lamivudine (LAM) daily (LAM group), 34 patients did not take any nucleos(t)ide analogue (non-NAs group), and the remaining 41 ACLF patients were not in the regime of this study who required others nucleos(t)ide analogue strategy, such as telbivudine, adefovir, LAM plus ADV, 1.0 mg ETV daily. All eligible patients were given standard medical treatment in the intensive care unit, including absolute rest on bed, energy supplements and vitamins, intravenous drop infusion albumin and plasma, electrolyte and acid–base equilibrium, and prevention and treatment of complications.

MELD-Na score

The serum creatinine level, INR for prothrombin time, the total serum bilirubin level, and the serum sodium concentration of each ACLF patient were recorded on the day of admission. The MELD-Na score was calculated using the following formula [8]: $3.78 \times \log_e$ (bilirubin [mg/dL]) + $11.2 \times \log_e$ (INR) + $9.57 \times \log_e$ (creatinine [mg/dL]) + $6.43 + 1.59 \times (135 - \text{Na [mEq/L]})$. The maximal serum creatinine level considered in the MELD-Na score equation

was 4.0 mg/dL, with the maximum and minimum Na values of 135 and 120 mEq/L, respectively.

Measurement of HBV marker, HBV DNA, and YMDD mutations

HBs-Ag, HBs-Ab, HBe-Ag, and HBe-Ab were detected by a qualitative enzyme immunoassay. Serum HBV DNA was measured by real-time polymerase chain reaction (PCR) assay. The detection limit was 1×10^3 IU/mL. HBV DNA levels of the patients were evaluated before and after the 3-week treatment. The tyrosine (Y), methionine (M), aspartate (D), and aspartate (D) motif mutant (YMDD motif mutant) were detected every 3–6 months by PCR assay during the follow-up period, with the lower limit of detection being approximately 1×10^4 IU/mL.

Follow-up

The patients were observed every 1–2 weeks for the first 3 months and every 3–6 months thereafter until October 2010. The clinical and laboratory data, adverse events, and compliance of all patients were recorded.

Statistical analysis

Quantitative data were expressed as mean ± standard deviation (SD) or median and range. One-way analysis of variance (ANOVA), *t*-test, or the nonparametric Mann–Whitney *U* test was used. A chi-squared test or Fisher's exact test were performed for comparison of qualitative data. A P value <0.05 was considered to indicate statistical significance. Data were analyzed using the Statistical Product and Service Solution (SPSS) software version 11.5 for Windows.

Results

Clinical backgrounds of the patients

One hundred and six consecutive patients with ACLF were enrolled and divided into three groups (ETV group, LAM group, and non-NAs group), as mentioned above. Background data of the patients in each group are shown in Table 1.

There were no significant differences between the three groups in the baseline characteristics of age, gender, serum ALT, AST, ALB, GLB, TBIL, CHE, CREA, INR, MELD score, and complications. The baseline HBV DNA level was much higher in the ETV group and LAM group than that in the non-NAs group ($P = 0.036$).

HBV DNA level

After 3 weeks of nucleoside analogue treatment and/or supportive therapy, the HBV DNA levels were decreased, when compared with the baseline level, in the ETV group (7.04 ± 1.58 $\log_{10}$ IU/mL vs. 4.03 ± 2.04 $\log_{10}$ IU/mL,

Table 1 Demographic data and baseline characteristics

	ETV M (SD)	LAM M (SD)	non-NAs M (SD)	*P* value
Male (%)	32 (76.2)	24 (80.0)	28 (80.2)	0.79
Age (years)	39.02 (13.04)	42.3 (9.57)	41.03 (11.95)	0.52
HBV DNA Log10 (IU/mL)	7.04 (1.58)	7.25 (0.89)	5.73 (0.96)	0.036
Cirrhosis (%)	23 (54.8)	21 (70)	16 (47.1)	0.173
ALT (U/L)	324.19 (310.04)	287.61 (261.50)	473.75 (655.76)	0.38
TBIL (μM/L)	326.29 (201.35)	332.65 (182.65)	312.10 (223.86)	0.95
ALB (g/L)	31.45 (5.79)	29.59 (5.63)	30.02 (6.82)	0.49
GLU (mM/L)	5.14 (1.82)	4.92 (2.85)	5.68 (3.03)	0.69
CHOL (mM/L)	1.63 (0.75)	1.47 (0.66)	1.78 (1.06)	0.51
CREA (μM/L)	85.39 (31.31)	89.33 (24.82)	73.80 (17.05)	0.25
K (mM/L)	4.64 (0.86)	4.41 (1.17)	4.28 (0.73)	0.48
PTA (%)	34.88 (12.27)	32.18 (11.44)	34.69 (13.89)	0.33
INR	1.97 (0.57)	2.04 (0.66)	1.94 (1.12)	0.92
FIB (g/L)	1.36 (0.48)	1.39 (0.66)	1.39 (0.40)	0.97
PLT (10^9/L)	88.66 (54.70)	81.30 (44.88)	102.33 (52.34)	0.52
WBC (10^9/L)	5.59 (2.53)	6.52 (4.17)	5.39 (2.79)	0.49
RBC (10^{12}/L)	3.74 (0.86)	3.42 (1.01)	3.65 (0.89)	0.44
MELD-Na	26.69 (12.09)	28.53 (10.85)	31.55 (14.01)	0.11

ETV enticavir, *LAM* lamivudine, *ALT* alanine aminotransferase, *TBIL* total bilirubin, *ALB* albumin, *GLU* glucose, *CHOL* cholesterol, *CREA* creatinine, *K* potassium, *PTA* prothrombin activity, *INR* international normalized ratio, *FIB* fibrinogen, *PLT* platelet count, *WBC* white blood cell count, *RBC* red blood cell count

$P = 0.001$), the LAM group (7.25 ± 0.89 $\log_{10}$ IU/mL vs. 4.33 ± 2.48 $\log_{10}$ IU/mL, $P = 0.01$), and the non-NAs group (5.73 ± 0.96 $\log_{10}$ IU/mL vs. 4.21 ± 1.47 $\log_{10}$ IU/mL, $P = 0.01$).

A significantly high proportion of patients acquired a >2 log10 IU/mL decrease in HBV DNA in the ETV group (81.3% vs. 42.9%, $P = 0.013$) and LAM group (80% vs. 42.9%, $P = 0.031$), compared with that in the non-NAs group.

A large proportion of patients in the antiviral therapy treatment group (ETV group + LAM group) acquired undetectable HBV DNA levels (1×10^3 IU/mL), when compared with that in the non-NAs group (69.2% vs. 35.7%, $P = 0.025$).The rate of the undetectable HBV DNA level after 1 month of treatment was significantly higher in the ETV group than in the non-NAs group (75.0% vs. 37.7%, $P = 0.014$). However, no statistically significant difference was detected between the ETV and LAM groups (75.0% vs. 60.0%, $P = 0.202$) and between the LAM and non-NAs groups (60.0% vs. 37.7%, $P = 0.148$).

Short-term survival

During the first month of treatment, a total of 39 patients died, 9 (21.4%) in the ETV group, 10 (33.3%) in the LAM group, and 20 (58.8%) in the non-NAs group; 1 patient in the ETV group was transferred to the liver transplantation center for orthotopic liver transplantation. In the second month, 2 patients in the ETV group accepted liver transplantation; a total of 6 patients died, 4 in the ETV group, 1 in the LAM group, and 1 in the non-NAs group. In the third month, 2 patients died, 1 in the LAM group and 1 in the non-NAs group. In the first 3 months, a total of 3 patients received liver transplantation and all of them were from the ETV group; forty-seven patients died. The ETV and LAM groups had a similar accumulative mortality during the first 3 months of treatment (33.3% vs. 40%, $\chi^2 = 0.568$, $P = 0.374$). However, the non-NAs group had a significantly high mortality, compared with the ETV group (64.7% vs. 33.3%, $\chi^2 = 7.163$, $P = 0.007$), the LAM group (64.7% vs. 40%, $\chi^2 = 3.906$, $P = 0.042$), and the nucleoside analogue group (ETV group + LAM group) (64.7% vs. 36.2%, $\chi^2 = 7.443$, $P = 0.006$).

Prognostic factors associated with short-term mortality

We compared the pretreatment data including age, HBV-related marker, total bilirubin, liver function, creatinine, PTA, MELD-Na score, and antiviral treatment strategy between patients who expired within 3 months and those who survived more than 3 months (Table 2). Univariate analyses indicate that TBIL > 171 μM/L ($P = 0.007$), CHOL < 1.7 mM/L ($P = 0.002$), PTA < 30% ($P = 0.001$), without NAs treatment ($P = 0.006$), CREA > 146 μM/L ($P = 0.004$), and MELD-Na score > 25 ($P = 0.001$) were the significant predictors of early mortality.

Long-term outcome of nucleoside analogue treatment

Of the 106 patients, 47 patients died within the first 3 months of nucleoside analogue treatment, 3 patients were transferred to the liver transplantation center for orthotopic liver transplantation, 56 patients survived. All the 56 patients were followed up until death or until October 2010. The median follow-up period was 7.3 months. Recurrence was observed in a total of 6 (10.72%) patients, 4 (33.33%) in the non-NAs group, 2 (11.11%) in the LAM group after the LAM therapy was terminated by patients themselves, and 0 in the ETV group ($P = 0.003$). Those results indicate that the risk of recurrence may be reduced by continuous nucleoside analogue treatment. No YMDD drug-resistant mutant was detected in the survivors during the follow-up period.

Table 2 Comparisons of baseline characteristic between survivors and non-survivors after 3 months treatment

	Non-survivor ($n = 47$)		Survivor ($n = 56$)		P value
	Mean	SD	Mean	SD	
Age (years)	41.29	12.25	40.06	12.35	0.720
HBV DNA ($\log_{10}$ IU/mL)	7.02	1.19	6.92	1.44	0.822
ALT (U/L)	273.94	332.60	358.65	393.79	0.440
GGT (U/L)	56.31	27.00	100.98	80.92	0.034
TBIL (μM/L)	402.71	235.42	297.28	178.03	0.049
ALB (g/L)	29.85	6.20	30.77	5.85	0.589
Na (mEq/L)	135.15	3.16	132.84	5.81	0.135
CHOL (mM/L)	1.21	0.44	1.72	0.83	0.022
SL	1.80	1.15	1.31	0.71	0.042
CREA (μM/L)	101.75	40.01	79.32	19.74	0.003
PTA (%)	36.22	9.10	48.70	20.25	0.067
MELD-Na	27.00	6.10	22.17	5.19	0.003

ALT alanine aminotransferase, *GGT* γ-glutamyltransferase, *TBIL* total bilirubin, *ALB* albumin, *Na* natrium, *CHOL* cholesterol, *SL* AST/ALT, *CREA* creatinine, *PTA* prothrombin activity

Discussion

HBV infection is one of the major causes of ACLF in China. In most patients with liver diseases, ACLF is triggered by cirrhotic complication such as spontaneous bacteria peritonitis and upper GI bleeding [6, 9, 10]. In patients with chronic hepatitis B, severe acute exacerbation is another important cause of ACLF [11]. The pathogenesis of ACLF remains incomplete understood [12]. A "two-hit" hypothesis may be proposed to partially explain the pathogenesis of ACLF: the first hit is considered to be the primary injury caused by HBV, and the second one is the host' imbalanced reaction to these initiating factors [13].

HBV replication is one of the key factors causing severe liver damage. High virus load is associated with rapidly progression and HCC [14]. Early antiviral treatment shortens and improves the symptomatic phase of infection and allows for a ready clinical and biochemical improvement [11, 15, 16]. Lamivudine, a nucleotide analogue binding to reverse transcriptase, has been proven effective in suppressing viral replication, improving histology and biochemical, and decreasing the inflammatory response. Lamivudine treatment has been shown to benefit patients with HBV-related decompensated cirrhosis and patients with ACLF in Hong Kong [17] and Taiwan [18]. However, the emergence of HBV mutant during the long-term lamivudine treatment hinders its clinical use. Enticavir is a carbocyclic analogue inhibiting HBV replication at three different steps [19]. Enticavir is more potent than lamivudine; it is effective against lamivudine-resistant mutants [20]. With the emergence of new, effective antiviral drugs with a high barrier to resistance, lamivudine is no longer recommended as a first-line treatment for chronic hepatitis B because of the high rate of drug resistance [3, 4], which prompted us to evaluate this agent in a series of patients with HBV-related ACLF.

Here, we conducted a retrospective study on 106 consecutive patients with ACLF. To the authors' knowledge, this is one of the biggest single-center experiences of the use of antiviral treatment to date. The patients were informed by clinical physicians of the difference between nucleos(t)ide analogues and the importance of long-term treatment. The HBV DNA load was much higher in the ETV and LAM groups than in the non-NAs group ($P = 0.036$). After 1 month of treatment, HBV DNA decreased in all three ACLF groups, more patients achieved a >2 log10 IU/mL decrease in HBV DNA and an undetectable HBV DNA level in the ETV group than in the non-NAs group. ETV and ALM effectively decreased the HBV DNA load. It was not surprising that HBV DNA load decreases in NAs treatment group. The reason for the decreased HBV DNA load in the non-NAs group is partially explained by the continuously stimulated immune system in the process of clearing HBV and reducing the replication space (hepatocytes) in the setting of massive or sub-massive hepatic necrosis [21–23].

The term of ACLF was first used in 1995 to describe the condition in which two insults to liver are operating simultaneously: one of them being ongoing and chronic and the other being acute. ACLF was insult with the underlying cirrhotic or without (acute exacerbation). Patients with the underlying decompensated cirrhosis have a better prognosis than those with severe acute exacerbation of cirrhosis (in-hospital mortality about 75%) [24]. In our study, the 3-month survival rate in the ETV, LAM, and non-NAs groups was 66.7, 60.0, and 35.3%, respectively. The ETV and LAM groups showed a higher survival rate than the non-NAs group. However, Cui et al. [6] reported that the 3-month survival rates were 48.49, 50.00, and 40.54% in patients treated with ETV, LAM, and non-NAs, respectively, and that no significant difference in the 3-month survival rate was detected between the nucleoside analogue treatment (ETV + LAM) and non-NAs treatment, albeit a slight trend toward superiority of the nucleoside analogue treatment over the non-NAs treatment. The discordance may result from the relatively small sample sizes used in Cui's and our studies. Relatively fewer patients with severe acute exacerbation were used in our study.

The high mortality in the non-NAs group is likely to be related to the failure of HBV eradication at an early stage. HBV continuously stimulates the immune system recruiting proinflammatory factor. Moreover, the elevated HBV DNA loads continuously activate liver NKT cells, which impair liver regeneration. A study from Germany shows that markers of liver injury were highly elevated in patients with HBV-related liver failure after only 1 week of enticavir treatment, leading to a significant decline in cell death and necrosis. We found that high total bilirubin, high serum creatinine, low CHOL, low PTA, non-nucleos(t)ide analogue treatment, and high MELD-Na score were significant predictors of early mortality, which is in consistent with a prospective study from Belgium [25].

A proportion of patients who received no nucleos(t)ide analogue treatment may repeat similar episodes of ACLF and have unfavorable prognosis even if they recover from the serious episodes. Nucleotide analogue treatment may bring long-term benefits with less recurrence. Clinicians should also be aware that HBV DNA is inhibited to an undetectable level but is not eliminated. Hepatitis flares may occur after withdrawal of treatment. Therefore, long-term treatment is recommended for patients with ACLF.

In conclusion, our study shows that short-term antiviral treatment with entecavir or lamivudine rapidly suppressed HBV replication, increased the short-term survival rate, and reduced recurrence. Early administration of long-term nucleoside analogue treatment is recommended for the

prevention of recurrence of HBV-related ACLF. This study shows its weakness in that it is a retrospective review of a single-center experience of a small number of samples. A prospective, randomized, double-blind, placebo-controlled trial of NAs in ACLF patients is needed to validate the present results.

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Conflict of interest None.

References

1. Stravitz RT, Kramer DJ (2009) Management of acute liver failure. Nat Rev Gastroenterol Hepatol 6:542–553
2. Sarin SK, Kumar A, Almeida JA, Chawla YK, Fan ST, Garg H, de Silva HJ, Hamid SS, Jalan R, Komolmit P, Lau GK, Liu Q, Madan K, Mohamed R, Ning Q, Rahman S, Rastogi A, Riordan SM, Sakhuja P, Samuel D, Shah S, Sharma BC, Sharma P, Takikawa Y, Thapa BR, Wai CT, Yuen MF (2009) Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). Hep Int 3:269–282
3. [Anon], Liver EAS (2009) EASL clinical practice guidelines: management of chronic hepatitis B. J Hepatol 50:227–242
4. Lok ASF, McMahon BJ (2009) Chronic hepatitis b: update 2009. Hepatology 50:661–662
5. Polson J, Lee WM (2005) AASLD position paper: the management of acute liver failure. Hepatology 41:1179–1197
6. Cui YL, Yan F, Wang YB, Song XQ, Liu L, Lei XZ, Zheng MH, Tang H, Feng P (2010) Nucleoside analogue can improve the long-term prognosis of patients with hepatitis B virus infection-associated acute on chronic liver failure. Dig Dis Sci 55:2373–2380
7. Chen J, Han JH, Liu C, Yu RH, Li FZ, Li QF, Gong GZ (2009) Short-term entecavir therapy of chronic severe hepatitis B. Hepatobiliary Pancreat Dis Int 8:261–266
8. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, Benson J, Therneau T, Kremers W, Wiesner R, Kamath P, Klintmalm G (2006) Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology 130:1652–1660
9. Sun LJ, Yu JW, Zhao YH, Kang P, Li SC (2010) Influential factors of prognosis in lamivudine treatment for patients with acute-on-chronic hepatitis B liver failure. J Gastroenterol Hepatol 25:583–590
10. Hsu CY, Lin HC, Huang YH, Su CW, Lee FY, Huo TI, Lee PC, Lee JY, Lee SD (2010) Comparison of the model for end-stage liver disease (MELD), MELD-Na and MELDNa for outcome prediction in patients with acute decompensated hepatitis. Dig Liver Dis 42:137–142
11. Wong VWS, Wong GLH, Yiu KKL, Chim AML, Chu SHT, Chan HY, Sung JJY, Chan HLY (2011) Entecavir treatment in patients with severe acute exacerbation of chronic hepatitis B. J Hepatol 54:236–242
12. Zhang Z, Zou ZS, Fu JL, Cai L, Jin L, Liu YJ, Wang FS (2008) Severe dendritic cell perturbation is actively involved in the pathogenesis of acute-on-chronic hepatitis B liver failure. J Hepatol 49:396–406
13. Williams CD, Bajt ML, Farhood A, Jaeschke H (2010) Acetaminophen-induced hepatic neutrophil accumulation and inflammatory liver injury in CD18-deficient mice. Liver Int 30:1280–1292
14. Manizate F, Fiel MI, Schwartz ME, Labow DM, Roayaie S, Dieterich D, Luan W, Hiotis SP (2010) Intrahepatic Cccdna burden and severity of hepatic fibrosis in patients with Hbv-associated Hcc. J Hepatol 52:S220
15. Zoulim F, Locarnini S (2009) Hepatitis B virus resistance to nucleos(t)ide analogues. Gastroenterology 137:1593–1608
16. Vallet-Pichard A, Mallet V, Costentin CE, Pol S (2009) Treatment of HBV-related cirrhosis. Expert Rev Anti Infect Ther 7:527–535
17. Chan AC, Fan ST, Lo CM, Liu CL, Chan SC, Ng KK, Yong BH, Chiu A, Lam BK (2009) Liver transplantation for acute-on-chronic liver failure. Hep Int 3:571–581
18. Chan PC, Chen HL, Kong MS, Huang FC, Lee HC, Lin CC, Liu CC, Lee IH, Wu TC, Wu SF, Ni YH, Hsu HY, Chang MH (2005) Factors affecting the mortality of pediatric fulminant hepatic failure in relation to hepatitis B virus infection. J Gastroenterol Hepatol 20:1223–1227
19. Schiff E, Simsek H, Lee WM, Chao YC, Sette H Jr, Janssen HL, Han SH, Goodman Z, Yang J, Brett-Smith H, Tamez R (2008) Efficacy and safety of entecavir in patients with chronic hepatitis B and advanced hepatic fibrosis or cirrhosis. Am J Gastroenterol 103:2776–2783
20. Ghany MG, Doo EC (2009) Antiviral resistance and hepatitis B therapy. Hepatology 49:S174–S184
21. Bartholomeusz A, Locarnini S (2006) Hepatitis B virus mutations associated with antiviral therapy. J Med Virol 78:S52–S55
22. Doo E, Liang TJ (2001) Molecular anatomy and pathophysiologic implications of drug resistance in hepatitis B virus infection. Gastroenterology 120:1000–1008
23. Barile M, Valenti D, Passarella S, Quagliariello E (1997) 3′-Azido-3′-deoxythymidine uptake into isolated rat liver mitochondria and impairment of ADP/ATP translocator. Biochem Pharmacol 53:913–920
24. Chan HLY (2010) Antiviral therapy for acute-on-chronic liver failure in chronic hepatitis B: is it too late? Dig Dis Sci 55:2126–2128
25. Katoonizadeh A, Laleman W, Verslype C, Wilmer A, Maleux G, Roskams T, Nevens F (2010) Early features of acute-on-chronic alcoholic liver failure: a prospective cohort study. Gut 59:1561–1569