Original Article

Meta-analysis on Treatment of Chronic Hepatitis B with Telbivudine and Entecavir

Zhen Ye¹, Min Zhao¹, He Jiao², Yang Feng¹, Ying-zi Li¹, Cui-fang Nie¹, Yan-mei Zhang¹, Bo Zhang¹, Shu-Lian Zhao¹, Zheng-hua Zhao¹ and Guang-ju Meng¹

Objective To evaluate the therapeutic effects of telbivudine and entecavir on patients with chronic hepatitis B by meta-analysis method.

Methods Databases including the Cochrane Library, PubMed, EMBASE and HighWire were searched from January 2008 to October 2012. Randomized controlled trials on treatment of chronic hepatitis B with telbivudine and entecavir were included. According to the Cochrane systematic reviews, the methodological quality of the included studies was evaluated and effective data was extracted from these studies and analyzed.

Results Six studies were included eventually. The telbivudine group included 417 cases and the entecavir group included 396 cases. For 12-week antiviral treatment of chronic hepatitis B, the rate of undetectable HBV DNA was 39.1% with telbivudine and 38.6% with entecavir [OR = 1.04, 95% CI (0.62, 1.73), $P > 0.05$]; for treatment of HBeAg (+) hepatitis B, the HBeAg clearance rate was 23.8% with telbivudine and 3.8% with entecavir [OR = 8.07, 95% CI (2.69, 24.21), $P < 0.05$], and the HBeAg seroconversion rate was 6.7% with telbivudine and 3.8% with entecavir [OR = 4.95, 95% CI (1.60, 15.31), $P < 0.05$]; the ALT normalization rate was 54.3% with telbivudine and 58.5% with entecavir [OR = 0.84, 95% CI (0.49, 1.45), $P > 0.05$]; and for early-stage treatment, the incidence of adverse events was 17.2% with telbivudine and 22.0% with entecavir [OR = 0.66, 95% CI (0.33, 1.32), $P > 0.05$]. For 1-year antiviral treatment of chronic hepatitis B, the rate of undetectable HBV DNA was 79.4% with telbivudine and 89.7% with entecavir [OR = 0.46, 95% CI (0.28, 0.74), $P < 0.05$]; for treatment of HBeAg (+) hepatitis B, the HBeAg clearance rate was 28.9% with telbivudine and 15.6% with entecavir [OR = 2.21, 95% CI (1.06, 4.58), $P < 0.05$], and the HBeAg seroconversion rate was 31.2% with telbivudine and 18.5% with entecavir [OR = 2.31, 95% CI (1.23, 4.31), $P < 0.05$]; the ALT normalization rate was 85.8% with telbivudine and 84.9% with entecavir [OR = 0.90, 95% CI (0.29, 2.84), $P > 0.05$]; and the resistance rate was 6.0% with telbivudine and 0.76% with entecavir [OR = 5.71, 95% CI (1.67, 19.47), $P < 0.05$].

Conclusions For 1-year treatment of chronic hepatitis B, the difference in ALT normalization between telbivudine and entecavir was not statistically significant; and telbivudine was superior over entecavir in terms of HBeAg undetectable and HBeAg seroconversion; entecavir was superior over telbivudine in terms of HBV DNA undetectable and resistance; and both drugs had similar rates of adverse events in early-stage treatment and no severe adverse event was noted. Both telbivudine and entecavir are effective antiviral drugs against hepatitis B.

Key words: Telbivudine; Entecavir; Hepatitis B; Meta-analysis

As reported by the World Health Organization, about 2 billion persons have been infected with HBV around the world, including 0.35 billion chronic HBV infected persons, and about 1 million persons died of liver cirrhosis, liver failure and HCC as a result of HBV infection every year.¹ Chronic hepatitis B is the most common cause of liver cirrhosis and hepatocellular carcinoma.² A persistent high level of HBV DNA is associated with the complications of hepatic cirrhosis and hepatocellular carcinoma. Antiviral drugs can effectively inhibit

the replication of the virus, reduce the inflammatory necrosis of the liver, and reduce liver complications.^{3,4} Oral administration of nucleotide analogues becomes the main way for antiviral treatment of hepatitis B, and this is mainly owing to their excellent virus inhibition effects, the convenience of single daily dose, as well as few adverse events.⁵ The main difficulties encountered in treatment of chronic hepatitis B through oral administration of antiviral drugs are the demand of long-term treatment and the risk of resistance. The overall objective for treatment of chronic hepatitis B is as follows: to inhibit HBV for a long period of time as far as possible, alleviate the inflammatory necrosis of hepatocytes and liver fibrosis, and postpone and reduce

¹Division of Infectious Diseases, Central Hospital of Taian, Shandong 271000, China

²Taishan Medical University, Taian 271000, China

³Correspondence: Zhen Ye, E-mail: yezichess@163.com

the occurrence of liver decompensation, liver cirrhosis, HCC and complications, thereby improving the life quality and prolonging the survival time. Standard antiviral treatment shall be conducted so long as indications exist and the conditions are appropriate. So far, 5 HBV nucleoside (nucleotide) drugs are available in clinic: lamivudine, adefovir dipivoxil, entecavir, telbivudine and tenofovir dipivoxil. Telbivudine, which is a L-enantiomer of natural thymidine, can inhibit the activity of HBV DNA polymerase by competing with the 5'-adenosine of thymine, which is a natural substrate for HBV, and inhibits the replication of HBV through incorporation into HBV DNA to terminate the elongation of the HBV DNA chain. Entecavir is a cyclopentyl guanosine analogue; and as a new anti-HBV drug, it can inhibit the initiation of HBV DNA replication, the reverse transcription of the HBV DNA minus strand and the formation of the HBV DNA plus strand, and possesses a high virus inhibition capability. In order to further identify the therapeutic effects of telbivudine and entecavir and provide a basis for their reasonable administration in clinic, our study systemically evaluated the therapeutic effects and safety of the randomized controlled trials on treatment of chronic hepatitis B with either of telbivudine or entecavir.

DATA AND METHODS

Inclusion criteria

Study type

Randomized controlled trials (RCTs), in English.

Study object

Patients with chronic hepatitis B with antiviral treatment indications.

Intervention measures

The intervention group received telbivudine alone or in combination with a liver protectant, and the control group received entecavir alone or in combination with the liver protectant.

Measurement indices

The primary indices include the rate of undetectable HBV DNA, the rate of undetectable HBeAg, the HBeAg seroconversion rate, the ALT normalization rate and the resistance rate; and the secondary index is adverse events.

Exclusion criteria

Non-randomized controlled trials; fundamental studies; repetitive publications; randomized controlled trials from which no effective data can be extracted; complicated with HAV, HCV, HEV, HDV or HIV infections; and liver cancer, post-liver transplantation or decompensated liver diseases.

Retrieval strategies

Computer retrieval was carried out from Cochrane Library, PubMed, EMBASE and HighWire (from January 2008 to October 2012). Corresponding retrieval strategies and manners were adopted based on the characteristics of different databases. The search terms included "telbivudine", "entecavir", "HBV DNA" and "treatment".

Evaluation of literatures and extraction of data

The literatures were screened by two evaluators independently according to the predetermined inclusion criteria, and any disagreement between the two evaluators, if present, was solved through discussion with a third evaluator. Based on the quality evaluation standard set forth in Cochrane Handbook 5.0.1,⁶ the included literatures were evaluated in terms of the randomization method, allocation concealment, blinding, intent-to-treat analysis, and the results of follow-up and selective reporting.

Statistical analysis

The meta-analysis was conducted with the RevMan 5.0 software. First, the included studies were tested for heterogeneity, inspection level for $\alpha = 0.1$.

If no statistical heterogeneity was found between the studies ($P > 0.1$, $I^2 < 50\%$), then the studies were subjected to the meta-analysis by the fixed-effect model; on the contrary, if statistical heterogeneity was found between the studies ($P < 0.1$, $I^2 > 50\%$), the causes of the heterogeneity were analyzed. The studies without clinical heterogeneity but with statistical heterogeneity were subjected to the meta-analysis by the random-effect model. If the heterogeneity between two groups was too high or it was impossible to find out the data sources, the descriptive analysis was adopted. For enumeration data, the odds ratio (OR) was adopted for statistic analysis of therapeutic effects. All the effect sizes were provided in the form of 95% CI.

RESULTS

General characteristics and methodological quality evaluation of included studies

Through the preliminary retrieval, 12 literatures from Cochrane Library, 64 literatures from PubMed, 565 literatures from EMBASE, and 91 literatures from HighWire were found; and after the studies that did not fulfill the inclusion criteria were excluded, 6 studies were finally included.⁷⁻¹² The telbivudine group included 417 cases, and the entecavir group included 396 cases. The general characteristics and the methodological quality evaluation of the included studies are shown in Table 1 and Table 2.

Table 1. General characteristics of included studies

Included studies	Follow-up duration	Number of cases (treatment group/control group)	Treatment	Observation indices
Shi 2008	24 weeks	40/40	Telbivudine 600 mg/day Entecavir 0.5 mg/day	Rates of HBV DNA undetectable, ALT normalization, HBeAg undetectable and HBeAg seroconversion, adverse events
Zheng 2010	24 weeks	64/63	LdT: 600 mg/day ETV: 0.5 mg/day	Rates of HBV DNA undetectable, HBeAg undetectable HBeAg seroconversion, and ALT normalization
Dong 2010	12 weeks	23/21	LdT: 600 mg/day ETV: 0.5 mg/day	Rates of HBV DNA undetectable, ALT normalization
Tsai 2011	48 weeks	97/98	Telbivudine 600 mg/day Entecavir 0.5 mg/day	Rates of HBV DNA undetectable, ALT normalization, HBeAg seroconversion, adverse events, and resistance
Huang 2011	52 weeks	90/90	LdT: 600 mg/day ETV: 0.5 mg/day	Rates of HBV DNA undetectable, HBeAg undetectable and HBeAg seroconversion, ALT normalization, resistance
Azam 2012	52 weeks	103/84	LdT: 600 mg/day ETV: 0.5 mg/day	Rates of HBV DNA undetectable, HBeAg undetectable, ALT normalization, adverse events, and resistance

Table 2. Methodological quality evaluation of included studies

Included studies	Randomization method	Blinding	Allocation concealment	Lost to follow-up	ITT analysis	Results of selective reporting study
Shi 2008	Randomization but do not describe the method	Unknown	Unknown	None	Yes	Yes
Zheng 2010	Randomization and describe the method	Open-label	Unknown	Yes	Yes	Yes
Dong 2010	Randomization but do not describe the method	Unknown	Unknown	None	Yes	Yes
Huang 2011	Randomization but do not describe the method	Single-blind	Open	None	Yes	Yes
Tsai 2011	Randomization but do not describe the method	Unknown	Unknown	None	Yes	Yes
Azam 2012	Randomization but do not describe the method	Unknown	Unknown	None	Yes	Yes

Results of meta-analysis

Undetectable HBV DNA

For 12-week treatment, 3 studies¹⁰⁻¹² were included in total. The telbivudine group included 128 cases and the entecavir group included 127 cases. There was no statistical heterogeneity between the studies ($P = 0.17$, $I_2 = 43\%$), so the fixed-effect model was adopted for pooled analysis. The results show that the difference between the two groups was not statistically significant [$OR = 1.04$, 95% CI (0.62, 1.73), $P > 0.05$]. For 12-week treatment, the rate of undetectable HBV DNA was 39.1% with telbivudine and 38.6% with entecavir. For 1-year treatment, 3 studies⁷⁻⁹ were included in total. The telbivudine group included 282 cases and the entecavir group included 272 cases. There was no statistical heterogeneity between the studies ($P = 0.35$, $I_2 = 5\%$), so the fixed-effect model was adopted for

pooled analysis. The results show that the difference between the two groups was statistically significant [$OR = 0.46$, 95% CI (0.28, 0.74), $P < 0.05$]. For 1-year treatment, the rate of undetectable HBV DNA was 79.4% with telbivudine and 89.7% with entecavir (Figure 1).

HBeAg clearance

For 12-week treatment of HBeAg (+) hepatitis B, 2 studies^{10,12} were included in total. The telbivudine group included 105 cases and the entecavir group included 106 cases. There was no statistical heterogeneity between the studies ($P = 0.99$, $I_2 = 0\%$), so the fixed-effect model was adopted for pooled analysis. The results show that the difference between the two groups was statistically significant [$OR = 8.07$, 95% CI (2.69, 24.21), $P < 0.05$]. For 12-week treatment, the HBeAg clearance rate was 23.8% with telbivudine and

Figure 1. Forest plot analyzing telbivudine and entecavir in terms of undetectable HBV DNA.

Figure 2. Forest plot analyzing telbivudine and entecavir in terms of undetectable HBeAg in HBeAg (+) patients.

3.8% with entecavir. For 1-year treatment of HBeAg (+) hepatitis B, 1 study⁹ was included in total. The telbivudine group included 90 cases and the entecavir group included 90 cases. The results show that the difference between the two groups was statistically significant [OR = 2.21, 95% CI (1.06, 4.58), $P < 0.05$]. For 1-year treatment, the HBeAg clearance rate was 28.9% with telbivudine and 15.6% with entecavir (Figure 2).

HBeAg seroconversion For 12-week treatment of HBeAg (+) hepatitis B, 2 studies^{10,12} were included in total. The telbivudine group included 105 cases and the entecavir group included 106 cases. There was no statistical heterogeneity between the studies ($P = 0.94$, $I^2 = 0\%$), so the fixed-effect model was adopted for pooled analysis. The results show that the difference between the two groups was statistically significant

[OR = 4.95, 95% CI (1.60, 15.31), $P < 0.05$]. For 12-week treatment, the HBeAg seroconversion rate was 6.7% with telbivudine and 3.8% with entecavir. For 1-year treatment of HBeAg (+) hepatitis B, 2 studies^{7,9} were included in total. The telbivudine group included 109 cases and the entecavir group included 130 cases. There was no statistical heterogeneity between the studies ($P = 0.95$, $I^2 = 0\%$), so the fixed-effect model was adopted for pooled analysis. The results show that the difference between the two groups was statistically significant [OR = 2.31, 95% CI (1.23, 4.31), $P < 0.05$]. For 1-year treatment, the HBeAg seroconversion rate was 31.2% with telbivudine and 18.5% with entecavir (Figure 3).

ALT normalization

For 12-week treatment, 2 studies^{10,12} were included in total. The telbivudine group included 105 cases and

Figure 3. Forest plot analyzing telbivudine and entecavir in terms of HBeAg seroconversion in HBeAg (+) patients.

Figure 4. Forest plot analyzing telbivudine and entecavir in terms of ALT normalization.

the entecavir group included 106 cases. There was no statistical heterogeneity between the studies ($P = 0.71$, $I^2 = 0\%$). The results show that the difference between the two groups was not statistically significant [OR = 0.84, 95% CI (0.49, 1.45), $P > 0.05$]. For 12-week treatment, the ALT normalization rate was 54.3% with telbivudine and 58.5% with entecavir. For 1-year treatment, 3 studies⁷⁻⁹ were included in total. The telbivudine group included 282 cases and the entecavir group included 272 cases. There was statistical heterogeneity between the studies ($P = 0.008$, $I^2 = 79\%$), so the random-effect model was adopted for pooled analysis. The results show that the difference between the two groups was not statistically significant [OR = 0.90, 95% CI (0.29, 2.84), $P > 0.05$]. For 1-year treatment, the ALT normalization rate was 85.8% with

telbivudine and 84.9% with entecavir (Figure 4).

Adverse events

No severe adverse event was found for both telbivudine and entecavir. For adverse events in the early-stage treatment, 3 studies¹⁰⁻¹² were included in total. The telbivudine group included 128 cases and the entecavir group included 127 cases. There was no statistical heterogeneity between the studies ($P = 0.31$, $I^2 = 3\%$), so the fixed-effect model was adopted for pooled analysis. The results show that the difference between the two groups was not statistically significant [OR = 0.66, 95% CI (0.33, 1.32), $P > 0.05$]. For early-stage treatment, the incidence of adverse events was 17.2% with telbivudine and 22.0% with entecavir (Figure 5).

Figure 5. Forest plot analyzing telbivudine and entecavir in terms of early-stage adverse events.

Figure 6. Forest plot analyzing telbivudine and entecavir in terms of resistance.

Drug resistance

Three studies⁷⁻⁹ were included in total. The telbivudine group included 283 cases and the entecavir group included 264 cases. There was no statistical heterogeneity between the studies ($P = 0.58$, $I^2 = 0\%$), so the fixed-effect model was adopted for pooled analysis. The results show that the difference between the two groups was statistically significant [OR = 5.71, 95% CI (1.67, 19.47), $P < 0.05$]. For 1-year treatment, the resistance rate was 6.0% with telbivudine and 0.76% with entecavir (Figure 6).

DISCUSSION

Totally 6 literatures were collected and included in the analysis, wherein 1 literature is a report from an annual meeting on liver diseases. The 6 literatures have a low methodological quality. Only one of the literatures mentions the randomization method specifically, and the other 5 literatures mention randomization but do not describe the specific method. One of the literatures mentions blinding. No literature has a follow-up duration of up to 2 years. As shown by a study made in Taiwan, a persistent high level of HBV DNA is related to the increased incidence of liver cirrhosis, hepatocellular carcinoma, and death, but is not related to the HBeAg or ALT level. A final goal of treatment of chronic hepatitis B is to inhibit the progression of the disease and prolong the survival time of the patient, and the achievement of this goal requires persistent inhibition of HBV DNA¹³⁻¹⁵. As pointed out in the meta-analysis of Singal, after 1-year treatment in patients with decompensated liver cirrhosis, lamivudine and entecavir provided similar rates of undetectable HBV DNA which were 83% and 80%, respectively, while the rate of undetectable HBV DNA with adefovir

dipivoxil was only 41%.¹⁶ According to the meta-analysis of Dakin, after 1-year treatment of HBeAg positive chronic hepatitis B, the rate of undetectable HBV DNA was 94% with tenofovir dipivoxil, 73% with entecavir, 50% with adefovir dipivoxil and 38% with lamivudine.¹⁷ According to the meta-analysis of Woo, for 1-year treatment in HBeAg positive patients, tenofovir dipivoxil had the highest rate of undetectable HBV DNA which was up to 88%, and it had an ALT normalization rate of 66% and an HBeAg seroconversion rate of 20%; and entecavir was most effective in improving the liver histology, which was up to 56%, and it had a rate of undetectable HBV DNA of 61% and an ALT normalization rate of 70%.¹⁸ As found through our analysis, for 12-week treatment, the rate of undetectable HBV DNA was 39.1% with telbivudine and 38.6% with entecavir; and for 1-year treatment, the rate of undetectable HBV DNA was 79.4% with telbivudine and 89.7% with entecavir. The end point of treatment of chronic hepatitis B varies with different populations. In HBeAg-positive and HBeAg-negative patients, the ideal end point of treatment is sustained HBsAg loss with or without seroconversion to anti-HBs; and in HBeAg-positive patients, durable HBeAg seroconversion is a satisfactory end point.¹⁴ As reported by Singal, lamivudine, adefovir dipivoxil and entecavir provided similar rates of undetectable HBeAg and HBeAg seroconversion in 1-year treatment, wherein the rates of undetectable HBeAg and HBeAg seroconversion in 1-year treatment with entecavir were 21% and 11% respectively.¹⁶ According to the meta-analysis of Dakin, the difference in HBeAg seroconversion rate between the several nucleotide analogues was not statistically significant.¹⁷ According to the meta-analysis of Woo, in HBeAg-positive patients with 1-year treatment, the

HBeAg seroconversion rate with tenofovir was 20%.¹⁸ As found by our analysis, after 12-week treatment of HBeAg (+) hepatitis B, the HBeAg clearance rate was 23.8% with telbivudine and 3.8% with entecavir, and the HBeAg seroconversion rate was 6.7% with telbivudine and 3.8% with entecavir; after 1-year treatment of HBeAg (+) hepatitis B, the HBeAg clearance rate was 28.9% with telbivudine and 15.6% with entecavir, and the HBeAg seroconversion rate was 31.2% with telbivudine and 18.5% with entecavir; after 12-week treatment, the ALT normalization rate was 54.3% with telbivudine and 58.5% with entecavir; and after 1-year treatment, the ALT normalization rate was 85.8% with telbivudine and 84.9% with entecavir. For the end point of hepatitis B treatment and even the treatment conducted with a persistently potent nucleotide analogue, the clearance of HBsAg is rare.¹⁹ The antiviral treatment of chronic hepatitis B is restricted by resistance. The resistance to the antiviral treatment is an important factor that determines the success of long-term treatment of chronic hepatitis B. The resistance to nucleotide analogues is related to aggravation of liver diseases. Sequential therapy increases the emergence of multi-resistance.²⁰ The best choice that ensures the success of long-term treatment of chronic hepatitis B is to choose a potent drug with a barrier to resistance as the first-line treatment drug. The barrier to resistance is associated with the viral genetic barrier, drug potency, patient compliance, and viral adaptability or the like.²⁰ The resistance to lamivudine occurs frequently and is as high as 80% after 5 years of treatment.^{21,22} The cumulative rate of resistance to adefovir after 5 years of treatment is 29% in HBeAg (-) patients and 42% in HBeAg (+) patients.^{23,24} The resistance to telbivudine occurs slowly, but after 2 years of treatment, the resistance rate is 25% in HBeAg (+) patients and 11% in HBeAg (-) patients.²⁵ The resistance to entecavir is relatively low and is 1.2% after 6 years of treatment.²⁶ No resistance is found after 3 years of treatment with tenofovir dipivoxil.²⁷ In recent guidelines, low-resistance potent antiviral drugs such as entecavir and tenofovir dipivoxil tend to be used as first-line treatment drugs.^{14,15,28} After 1 year of treatment, the pooled analysis reveals that the resistance of 11% to lamivudine is significantly higher than the resistance of 0% to adefovir dipivoxil and the resistance of 0% to entecavir, and that the rate of severe adverse events of entecavir is 6%.¹⁶ As found through our analysis, after 1 year of treatment, the rate of resistance was 6.0% with telbivudine and 0.76% with entecavir; and at the early stage of treatment, the incidence of adverse events was 17.2% with telbivudine and 22.0% with entecavir, and no severe adverse event was found for both of them. The results of our study are different from those of foreign researchers, which

may be attributable to different populations, different disease severities and different viral genotypes.

LIMITATIONS

- All the literatures included in the study are from Asia and there is no literature from Europe and America, so bias may exist.
- The quality of the literatures included in the study is not high.
- The follow-up duration is short and no literature has a follow-up duration of up to 2 years.

CONCLUSIONS

For 1-year treatment of chronic hepatitis B, the difference in ALT normalization between telbivudine and entecavir was not statistically significant; telbivudine was superior over entecavir in terms of undetectable HBeAg and HBeAg seroconversion; entecavir was superior over telbivudine in terms of undetectable HBV DNA and resistance; and at the early stage of treatment, the two drugs had similar rates of adverse events and no severe adverse event was found for both of them. Both telbivudine and entecavir are effective antiviral drugs against hepatitis B.

REFERENCES

- Ganem D, Prince AM. Hepatitis B virus infection--natural history and clinical consequences. *N Engl J Med* 2004;350:1118-1129.
- Chan HL, Sung JJ. Hepatocellular carcinoma and hepatitis B virus. *Semin Liver Dis* 2006; 26:153-161.
- Wong VW, Wong GL, Chim AM, Choi PC, Chan AW, Tsang SW, et al. Surrogate end points and long-term outcome in patients with chronic hepatitis B. *Clin Gastroenterol Hepatol* 2009;7:1113-1120.
- Sung JJ, Tsoi KK, Wong VW, Li KC, Chan HL. Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2008;28:1067-1077.
- Wong VW, Wong GL, Tse CH, Yuen LK, Chan HY, Locarnini SA, et al. Antiviral drug resistance testing in patients with chronic hepatitis B. *Dig Dis Sci* 2012;57:221-231.
- Cochrane Handbook for Systematic Review of Interventions Version 5.0.2. The Cochrane Collaboration 2009;2:275.
- Tsai MC, Lee CM, Chiu KW, Hung CH, Tung WC, Chen CH, et al. A comparison of telbivudine and entecavir for chronic hepatitis B in real-world clinical practice. *J Antimicrob Chemother* 2012;67:696-699.
- Azam M, Khan M, Abdullah S, Sheikh R, Uddin A. Telbivudine and entecavir for adult chronic hepatitis B patients in Bangladesh: Results at 1 year. *Hepa Inter* 2012;6:127.
- Huang J, Chen XP, Chen XF, Chen WL, Chen R, Ma XJ, et al. Study on the efficacy and HBeAg seroconversion related factors of telbivudine and entecavir therapy in HBeAg positive chronic hepatitis B patients. *Zhonghua Gan Zang Bing Za Zhi* 2011;19:178-181.
- Zheng MH, Shi KQ, Dai ZJ, Ye C, Chen YP. A 24-week, parallel-group, open-label, randomized clinical trial comparing the early antiviral efficacy of telbivudine and entecavir in the treatment of hepatitis B e antigen-positive chronic hepatitis B virus infection in adult Chinese patients. *Clin Ther* 2010;32:649-658.

11. Suh DJ, Um SH, Herrmann E, Kim JH, Lee YS, Lee HJ, et al. Early viral kinetics of telbivudine and entecavir: results of a 12-week randomized exploratory study with patients with HBeAg-positive chronic hepatitis B. *Antimicrob Agents Chemother* 2010;54:1242-1247.
12. Shi KQ, Zhang DZ, Guo SH, He H, Wang ZY, Shi XF, et al. Short-term results of telbivudine versus entecavir treatments in HBeAg-positive chronic hepatitis B patients in China. *Zhonghua Gan Zang Bing Za Zhi (Chin)* 2008;16:641-645.
13. Zoulim F, Perrillo R. Hepatitis B: reflections on the current approach to antiviral therapy. *J Hepatol* 2008;48 Suppl 1:S2-19.
14. EASL Clinical Practice Guidelines: management of chronic hepatitis B. *J Hepatol* 2009;50:227-242.
15. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009;50:661-662.
16. Singal AK, Fontana RJ. Meta-analysis: oral anti-viral agents in adults with decompensated hepatitis B virus cirrhosis. *Aliment Pharmacol Ther* 2012;35:674-689.
17. Dakin H, Fidler C, Harper C. Mixed treatment comparison meta-analysis evaluating the relative efficacy of nucleos(t)ides for treatment of nucleos(t)ide-naïve patients with chronic hepatitis B. *Value Health* 2010;13:934-945.
18. Woo G, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M, Wong DK, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology* 2010;139:1218-1229.
19. Zoutendijk R, Hansen BE, van Vuuren AJ, Boucher CA, Janssen HL. Serum HBsAg decline during long-term potent nucleos(t)ide analogue therapy for chronic hepatitis B and prediction of HBsAg loss. *J Infect Dis* 2011;204:415-418.
20. Zoulim F. Hepatitis B virus resistance to antiviral drugs: where are we going? *Liver Int* 2011;31:111-116.
21. Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003;125:1714-1722.
22. Lai CL, Dienstag J, Schiff E, Leung NW, Atkins M, Hunt C, et al. Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B. *Clin Infect Dis* 2003;36:687-696.
23. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006;131:1743-1751.
24. Marcellin P, Chang TT, Lim SG, Sievert W, Tong M, Arterburn S, et al. Long-term efficacy and safety of adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *Hepatology* 2008;48:750-758.
25. Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, et al. 2-year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009;136:486-495.
26. Chang TT, Lai CL, Kew Yoon S, Lee SS, Coelho HS, Carrilho FJ, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology* 2010;51:422-430.
27. Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med* 2008;359:2442-2455.
28. Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int* 2008;2:263-283.