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Comparison of the forty-eight week efficacy between telbivudine and entecavir in HBeAg-positive Asian patients with chronic hepatitis B: A meta-analysis

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Background/aims: *Telbivudine and entecavir are two pharmacologic agents recommended and also widely used for the treatment of chronic hepatitis B in most Asian countries. There are few conclusive results when comparing the efficacy of these two drugs for the treatment of chronic hepatitis B. The aim of this study is to evaluate, by means of meta-analysis, the short-term efficacy between the two drugs in nucleos(t)ide-naïve Asian HBeAg-positive chronic hepatitis B patients.* ***Materials and Methods:*** *We searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, the Wanfang Database and CNKI (National Knowledge Infrastructure). Twelve eligible trials (1011 patients in total) were included into this study, and they were evaluated for quality and heterogeneity.* ***Results:*** *Meta-analysis date showed the rate of HBeAg clearance and rate of HBeAg seroconversion in the telbivudine group was higher than the entecavir group, respectively. There was no statistically significant difference however between the two groups in the rate of alanine aminotransferase normalization, or the rate of HBV DNA suppression. Although creatine kinase elevations occurred more frequently in the telbivudine group than when compared to the entecavir group, there was no statistically significant difference between the two groups in the short-term treatment duration.* ***Conclusions:*** *For the short-term treatment of HBeAg-positive nucleos(t)ide-naïve Asian patients with chronic hepatitis B, telbivudine is as potent as entecavir in normalizing alanine aminotransferase and suppressing HBV DNA, and telbivudine is superior to entecavir in clearing HBeAg and developing anti-HBe. Careful monitoring is needed to avoid adverse events, as well as drug resistance during antiviral therapy with telbivudine.*

Key words: HBeAg, telbivudine, entecavir

HBeAg pozitif kronik hepatit B'li Asya'lı hastalarda kırksekiz haftalık telbivudin ve entekavirin etkinliğinin karşılaştırılması: Bir meta-analiz

Giriş ve Amaç: *Telbivudin ve entekavir, bir çok Asya ülkesinde kronik hepatit B'li hastaların tedavisinde önerilse ve geniş kullanım alanı bulsa da, iki ilacın tedavideki etkinliğini karşılaştıran sonuçlar çok azdır. Bu çalışmanın amacı, metaanaliz yöntemi kullanılarak, nükleoz(t)id naif Asyalı HBeAg pozitif hastalarda iki ilacın kısa süreli etkinliklerini karşılaştırmaktır.* ***Gereç ve Yöntem:*** *Pubmed, Embase, the Cochrane Central Register of Controlled Trials, the Wanfang Database ve CNKI (National Knowledge Infrastructure) taranmıştır. Oniki uygun çalışma (toplam 1011 hasta) alınmış ve kalite ve heterojenite açısından değerlendirilmiştir.* ***Bulgular:*** *Meta-analiz göstermiştir ki, HBeAg temizlenmesi ve serokonversiyonu telbivudin tedavisinde entekavir grubuna göre daha fazla bulunmuştur. Ancak, iki grup arasında alanin aminotransferaz normalizasyonu ve HBV-DNA baskılanma yüzdesi açılarından fark bulunmamıştır. Telbivudin grubundaki kreatin kinaz yükselmeleri entekavir grubundan daha sık olsa da kısa süreli tedavide iki grup arasında fark bulunmamıştır.* ***Sonuç:*** *HBeAg pozitif nükleoz(t)id naif kronik hepatit B'li Asya'lı hastaların kısa süreli tedavisinde telbivudin, entekavire göre alanin aminotransferaz normalizasyonu ve HBV DNA baskılanması açılarından eş değer etkinlikteyken, HBeAg temizlenmesi ve anti-HBe gelişmesinde telbivudin entekavire göre daha etkilidir. Telbivudin ile tedavide yan etkiler ve ilaç direnci gelişmesi açısından dikkatli takip gereklidir.*

Anahtar kelimeler: HBeAg, telbivudin, entekavir

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INTRODUCTION

Hepatitis B is highly prevalent, with roughly 350 million chronic cases worldwide (1). According to the natural history of hepatitis B virüs (HBV), chronically infected individuals are at a high risk of death from cirrhosis and/or liver cancer with disease progression (2). The goal for treatment of chronic hepatitis B (CHB) is to reduce long-term complications and HBV-related mortality by suppressing HBV replication. The use of new antiviral drugs, such as nucleotide analogs offers the potential for improved prognosis of patients suffering from CHB (3). Up until the time in which this paper was written, five oral antiviral drugs are recommended for treatment of CHB. They are divided into two classes of drugs, named nucleoside analogs, which include lamivudine (LAM), telbuvidine (LdT), and entecavir (ETV), and nucleotide analogs, which include adefovir (ADV) and tenofovir (TDF). There are also standard alpha interferon and PEG-interferon treatments.

Although these agents have similar mechanisms of action, they have different efficacies as well as different characteristics. Recently, some studies with excellent evidence have been performed which compared these drugs as follows: LAM vs. ADV (4-6), LAM vs. ETV (7,8), LAM vs. LdT (9-11), ADV vs. ETV (12-14), ADV vs. LdT (15), ADV vs. TDF (16,17). In a study performed by Heathcote et al., it was reported that TDF and ETV are the two most potent oral antiviral agents for HBeAg-positive patients in the first year of treatment for CHB (18). Unfortunately, TDF has not been introduced to most financially-challenged countries, where there is high HBV rates (19) (HBsAg carriage >8%). Although LdT and ETV have been widely used in most Asian countries and both are regarded as oral antiviral agents with superior efficacy compared to other CHB treatments in China, there have been few large, high quality, multi-center trials to compare the efficacy of LdT and ETV. Therefore, we conducted this study utilizing meta-analysis to evaluate the efficacy of these two drugs in Asian nucleos(t)ide-naïve patients with known HBeAg-positive CHB.

MATERIALS and METHODS

Literature search

We searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, the Wanfang Database and CNKI (National Knowledge Infrastructure) from the date of inception to April 2011. Of the databases, the Wanfang Database and CNKI provided literature in Chinese. The search process was designed using the keywords “Hepatitis B”, “Telbivudine”, “Entecavir”. Reference lists from retrieved documents were also searched.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) study design: Must have been a randomized controlled trial or cohort study; (ii) study population: nucleos(t)ide-naïve Asian patients with HBeAg positive CHB; (iii) intervention consisting of LdT and ETV with dosages that were 600 mg/d and 0.5 mg/d, respectively, with the duration lasting ≥12 weeks.

The exclusion criteria from the study were as follows: (i) non-human studies; (ii) co-infection with hepatitis A, C, D, E or human immunodeficiency virus (HIV); (iii) co-existence of any other liver disease such as autoimmune hepatitis, alcoholic liver disease, drug induced hepatitis, etc.; (iv) liver transplantation; (v) past or current hepatocellular carcinomas.

Data extraction

Data was extracted independently by two authors (Sun Hang and Feng Qian) utilizing pre-defined forms, and the information was subsequently entered into Review Manager (Revman 5.1). The following information was then extracted: the type of study (including random sequence generation, blinding method, and description of withdrawals and dropouts), participants (including age range, sample size, gender), interventions, and concrete study results. Discrepancies were resolved by discussion amongst authors and utilizing the references to the original literature. If required, we attempted to contact the trial author for further details.

Outcome measures and definitions

The proportion of patients with biochemical, virological, and serological responses were then assessed. A biochemical response was defined as normalization of serum alanine aminotransferase (ALT). Virological response was defined as attainment of undetectable levels of serum HBV DNA by polymerase chain reaction (PCR). Serological response was assessed by HBeAg loss and seroconversion. HBeAg loss was defined as HBeAg clearance, while HBeAg seroconversion was defined as the appearance of anti-HBe. Virological resistance was defined as genotypic resistance of HBV, which was confirmed utilizing sequencing PCR.

Quality assessment

The quality of the inclusive studies was assessed using the JADAD scale.

Data analysis

Data analysis was carried out utilizing Revman 5.1 (Cochrane Collaboration, Oxford, United Kingdom). We used relative risk (RR) parameter of the main outcomes as the main measure of efficacy. A 95% confidence interval (CI) for the combined RR is also provided. Meta-analysis was performed using fixed-effect or random-effect methods, depending on the absence or presence of significant heterogeneity. Statistical heterogeneity between trials was evaluated utilizing Chi-square and I-square (I^2) tests, with significance set at $P<0.10$. In the absence of statistically significant heterogeneity, the fixed-effect method was used to combine the results. When heterogeneity was confirmed ($p<0.10$), the random-effect method was used. Additionally, sensitivity analysis was carried out if low quality trials were included into the study. The overall effect was tested using Z scores calculated by Fisher's Z' transformation, with significance set at $p<0.05$.

RESULTS

Characteristics and quality of studies

The electronic search yielded 1.215 citations. Of these studies in the search, 1.080 and 135 articles were published in English and Chinese, respectively. By scanning titles and abstracts, redundant publications, reviews, and meta-analyses were excluded. After referring to full texts, 12 clinical trials (20-31) satisfied the inclusion criteria as specified earlier, and this involved 1.011 patients in total. 505 patients were included in LdT groups and 506 patients in ETV groups. The main features and detailed information of the studies evaluated by meta-analysis are summarized in Tables 1 and 2.

Biochemical response

Seven trials were conducted that evaluated the 12-week biochemical response of LdT vs. ETV therapy. According to Chi-square and I square (I^2) results, heterogeneity was assessed and not found to be a concern. The relative risk of LdT vs. ETV was estimated by use of the fixed effect model. The 12-week biochemical response rates in the LdT group vs. the ETV group in the seven trials revealed no statistically significant difference [186/306 vs. 186/297, RR=0.97, 95%CI (0,85-1,09), p=0,58] (Figure 1). We next analyzed the 24-week data. Eight trials were included for the 24 week data evaluation. No statistical heterogeneity was found and again the fixed effect model was utilized. The 24-week result revealed no statistically significant difference in the two groups [262/342 vs. 251/333, RR=1,02, 95%CI (0,94-1,11), p=0,68] (Figure 2). When a 48-week data analysis was performed, no statistical heterogeneity was found, and again the fixed effect model was used. The 48-week result revealed no statistically significant difference between the two groups [251/297 vs. 250/287, RR=0,97, 95%CI (0,91-1,04), p=0,40] (Figure 3).

Virological response

Ten trials were conducted to evaluate the 12-week virological response of LdT vs. ETV therapy. Ac-

Table 1. Characteristics of the clinical trials included in the meta-analysis.

Study	Study design	Area	NA options	NA regimens (mg/day)	Treatment (weeks)
Ding 2009 (20)	RCT	Shan Dong, China	LdT vs. ETV	600 vs. 0.5	48
Huang 2011 (21)	RCT	Guang Dong, China	LdT vs. ETV	600 vs. 0.5	104
Liu 2010 (22)	RCT	An Hui, China	LdT vs. ETV	600 vs. 0.5	48
Zheng 2010 (23)	RCT	Zhe Jiang, China	LdT vs. ETV	600 vs. 0.5	24
Shi 2008 (24)	RCT	Chong Qing, China	LdT vs. ETV	600 vs. 0.5	24
Suh 2010 (25)	RCT	Seoul, Korea	LdT vs. ETV	600 vs. 0.5	12
Ye 2009 (26)	Cohort	Jiang Su, China	LdT vs. ETV	600 vs. 0.5	48
Yu 2010 (27)	RCT	Jiang Su, China	LdT vs. ETV	600 vs. 0.5	48
Zhang 2010 (28)	RCT	Guang Dong, China	LdT vs. ETV	600 vs. 0.5	72
Zhao 2009 (29)	RCT	Ji Lin, China	LdT vs. ETV	600 vs. 0.5	48
Zhou 2010 (30)	RCT	Guang Dong, China	LdT vs. ETV	600 vs. 0.5	48
Zhu 2011 (31)	RCT	Zhe Jiang, China	LdT vs. ETV	600 vs. 0.5	24

RCT, randomized controlled trial. NA: Nucleoside analog.

Table 2. Additional characteristics of the clinical trials included in the meta-analysis.

Study	Sample size (n) (LdT vs. ETV)	Gender (M:F) (LdT vs. ETV)	Age (Year) (LdT vs. ETV)	Mean ALT (U/L)	Mean HBV DNA (log10 copies/ml)
Ding 2009 (20)	60 (30 vs. 30)	17:13 vs. 18:12	(37.2±7.96) vs. (36.1±7.12)	(195±96.1) vs. (192±101.8)	(8.1±1.5) vs (8.0±1.7)
Huang 2011 (21)	180 (90 vs.90)	59:31 vs. 64:26	(28.8±9.8) vs. (31.0±1.0)	(150.6±91.0) vs. (163.1±105.7)	(6.87±0.97) vs (7.13±1.11)
Liu 2010 (22)	40 (20 vs. 20)	18:22	NA	NA	NA
Zheng 2010 (23)	131 (65 vs. 66)	49:16 vs. 42:24	(31.6±8.7) vs. (33.5±9.1)	(167.3±100.4) vs. (160.3±89.8)	(7.45±0.69) vs (7.51±0.85)
Shi 2008 (24)	80 (40 vs. 40)	29:11 vs. 25:15	(30.5±7.11) vs. (31.5±7.95)	(186.5±104.8) vs. (146.7±69.1)	(7.43±0.69) vs (7.57±0.51)
Suh 2010 (25)	44 (23 vs. 21)	18:5 vs. 12:9	(36.2±9.62) vs. (33.4±8.82)	(163.1±125.2) vs. (170.2±152.7)	(10.29±1.6) vs (9.72±1.7)
Ye 2009 (26)	92 (46 vs. 46)	33:13 (NA vs. NA)	NA	186 (NA vs NA)	NA
Yu 2010 (27)	177 (92 vs. 85)	NA	NA	NA	(6.91±2.14) vs (6.54±2.35)
Zhang 2010 (28)	140 (75 vs. 65)	59:16 vs. 50:15	(31.93±7.96) vs. (34.77±10.76)	(156.78±124.73) vs (165.14±131.61)	(6.90±0.99) vs (6.75±1.15)
Zhao 2009 (29)	72 (36 vs. 36)	56:16 (NA vs. NA)	34.3 (NA vs. NA)	NA	NA
Zhou 2010 (30)	115 (52 vs. 63)	72:43 (NA vs. NA)	46.3±9.0 (NA vs NA)	(197.2±38.2) vs (210.8±37.4)	(7.0±1.3) vs (6.9±1.0)
Zhu 2011 (31)	60 (30 vs. 30)	26:4 vs. 29:1	(28.0±9.1) vs (31.8±7.1)	(237.7±165.9) vs (423.7±501.8)	(7.07±0.80) vs (6.73±1.16)

LdT: Telbivudine. ETV: Entecavir. M: Male. F: Female. ALT: Alanine aminotransferase. HBV: Hepatitis B Virus.

cording to Chi-square and I square (I^2) results, no statistical heterogeneity was found in the comparison, and the fixed effect model was used. The 12-week virological response rates in the LdT group vs. ETV group in the ten trials showed no statistically significant differences [219/473 vs. 228/466, RR=0,95, 95%CI (0,83-1,08), p=0,40] (Figure 4). We also analyzed 24-week data. Ten trials were included in this evaluation. No statistical heterogeneity was found, and the fixed effect model was used. The 24-week results showed no statistically significant difference between the two groups [349/486 vs. 326/481, RR=1,06, 95%CI (0,98-1,15), p=0.17] (Figure 5). The 48-week data also showed no statistically significant difference between the two groups [365/441 vs. 363/435, RR=0.99, 95%CI (0,93-1,05), p=0,77] (Figure 6).

HBeAg loss

For this analysis, seven trials reported the 24-week rates of HBeAg loss. The results of the seven trials revealed that the 24-week HBeAg loss rate of the LdT group was 35,6%, while the ETV group rate was 24,9%. There was no statistical heterogeneity, and the fixed effect model was used. The difference in the 24-week HBeAg loss rate between the two groups achieved statistical significance [RR=1,42, 95%CI (0,37-1,74), p=0,004] (Figure 7). We also analyzed 48-week data. Only six trials were included for the 48 week analysis. No statistical heterogeneity was found, and the fixed effect model was used. The 48-week result also showed a statistically significant difference in the two groups [119/330 vs. 74/334, RR=1,58, 95%CI (1,24-2,00), p=0,0002] (Figure 8).

HBeAg seroconversion

In this analysis, eight trials reported the 24-week rates of HBeAg seroconversion. The results of the eight trials revealed that the 24-week HBeAg seroconversion rate of the LdT group was 22,0%, while the ETV group rate was 12,9%. There was no statistical heterogeneity, and the fixed effect model was used. The difference of the 24-week HBeAg seroconversion rate between the two groups achieved statistical significance [RR=1,71, 95%CI (1,25-2,33), p=0,0008] (Figure 9). We also analyzed the 48-week data for the same parameters. Eight trials were included in this analysis. No statistical heterogeneity was found, and the fixed effect model was used. The 48-week results also showed a statistically significant difference between the two groups [122/441 vs. 61/435, RR=1,91, 95%CI (1,45-2,51), p<0,00001] (Figure 10).

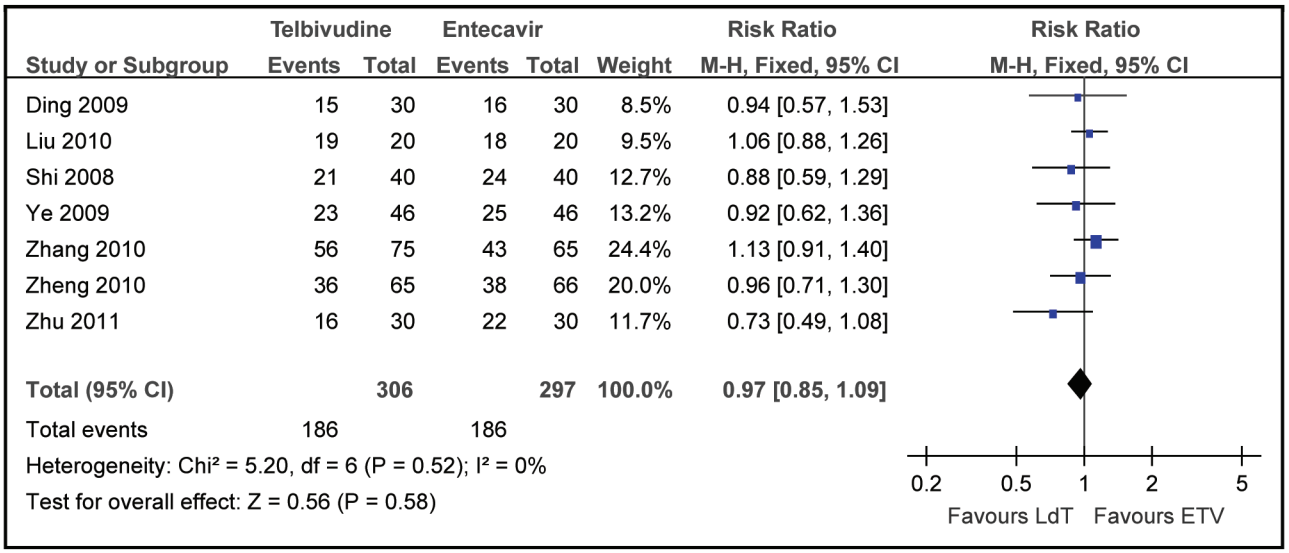

Figure 1. Forest plot of the 12-week biochemical response of LdT vs. ETV.

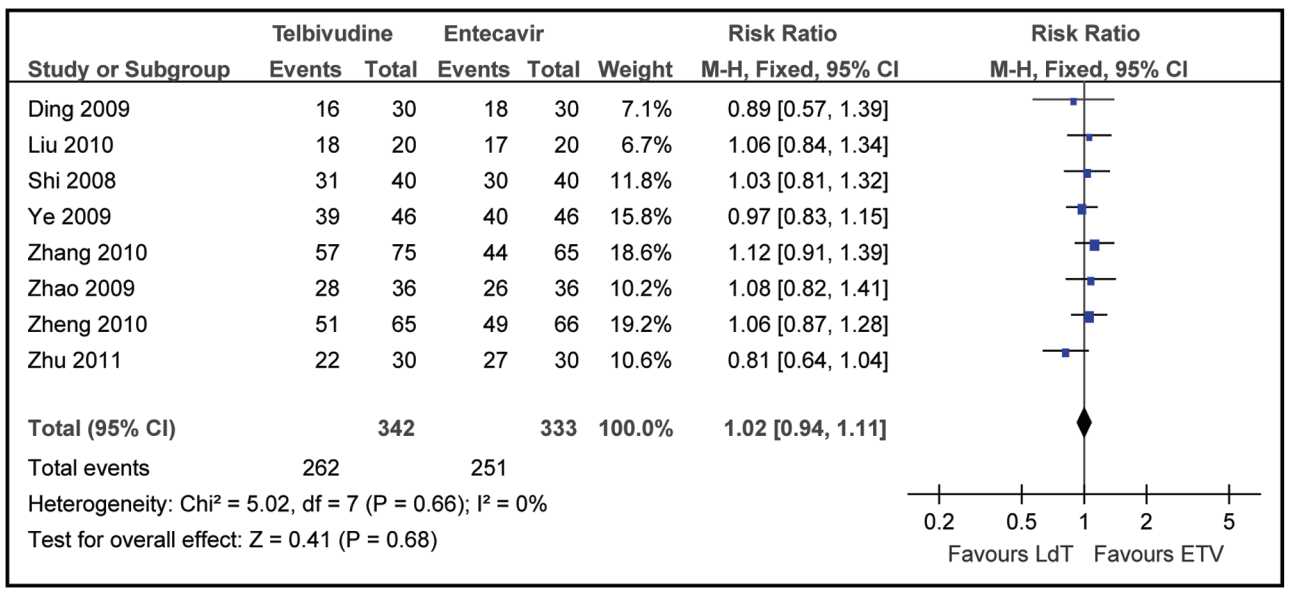

Figure 2. Forest plot of the 24-week biochemical response of LdT vs. ETV.

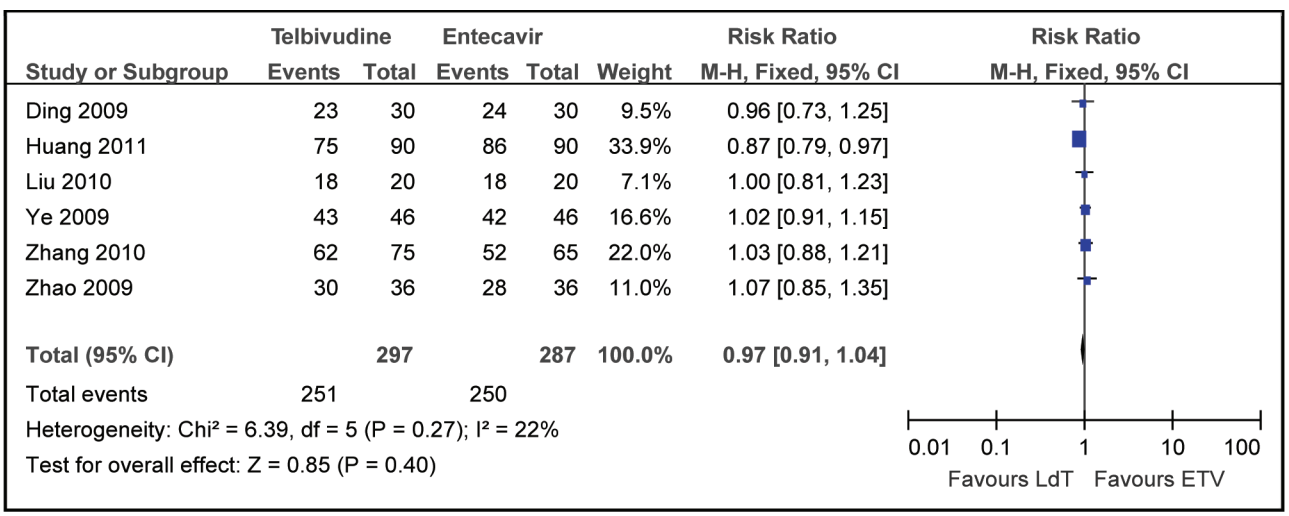

Figure 3. Forest plot of the 48-week biochemical response of LdT vs. ETV.

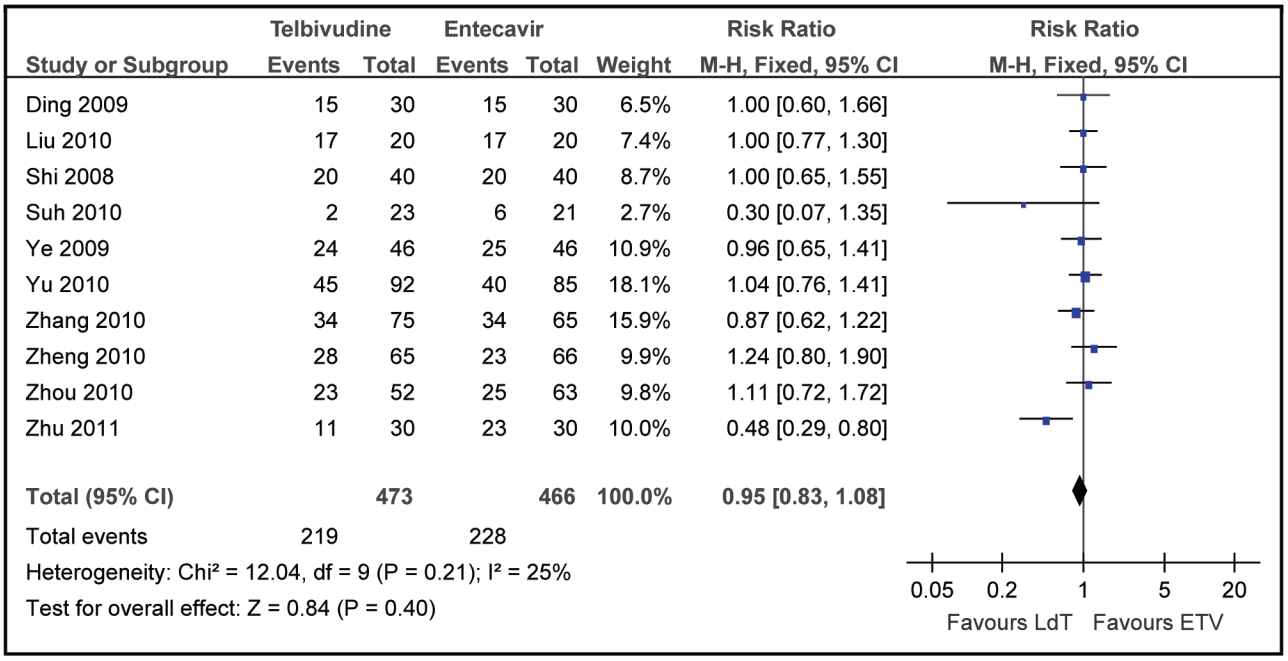

Figure 4. Forest plot of the 12-week virological response of LdT vs. ETV.

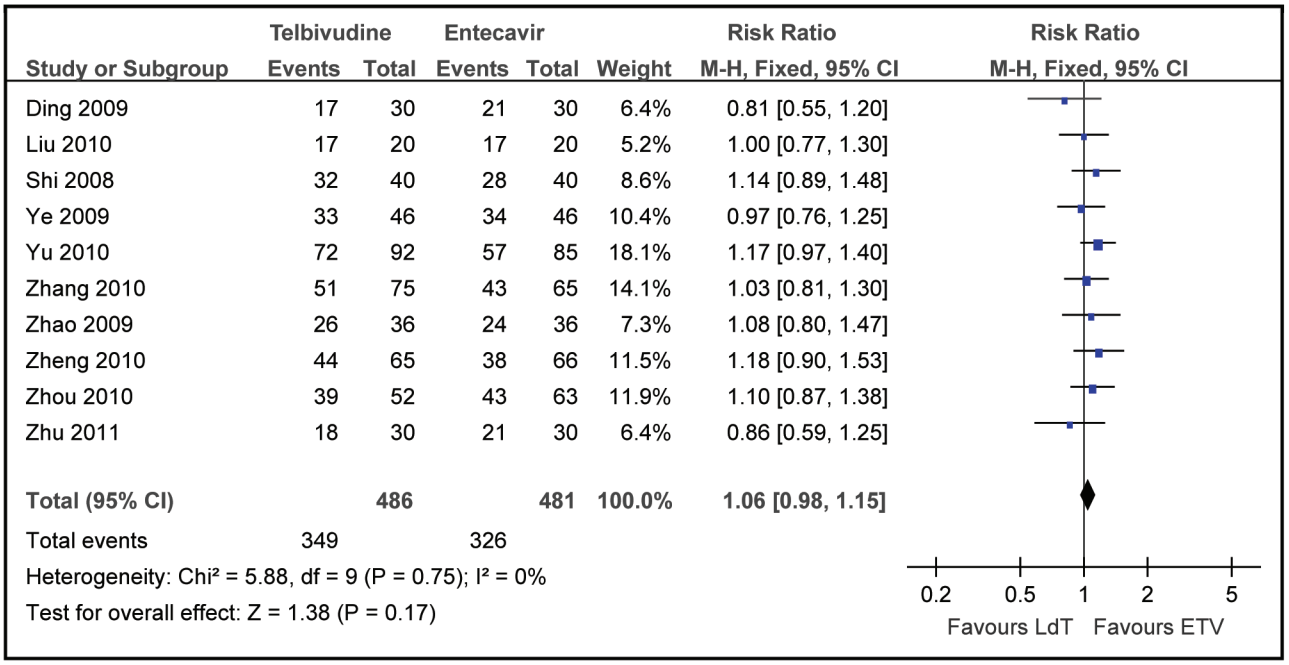

Figure 5. Forest plot of the 24-week virological response of LdT vs. ETV.

Drug resistance and safety

Four trials demonstrated the viral resistance rate during the treatment timeframe. The results showed that the rates for the LdT group and ETV group were 3,51% and 0,62%, respectively. No statistical heterogeneity was found in this comparison, and the fixed effect model was used. The results showed no statistically significant difference between the two groups [RR=2,89, 95%CI (0,71-11,73), p=0,14] (Figure 11).

Five trials reported creatine kinase (CK) elevation rates during the treatment. No statistical heterogeneity was found, and the fixed effect model was used. The result revealed a statistically significant difference in the two groups [31/213 vs. 6/202, RR=3,78, 95%CI (1,79-8,00), p=0,0005] (Figure 12).

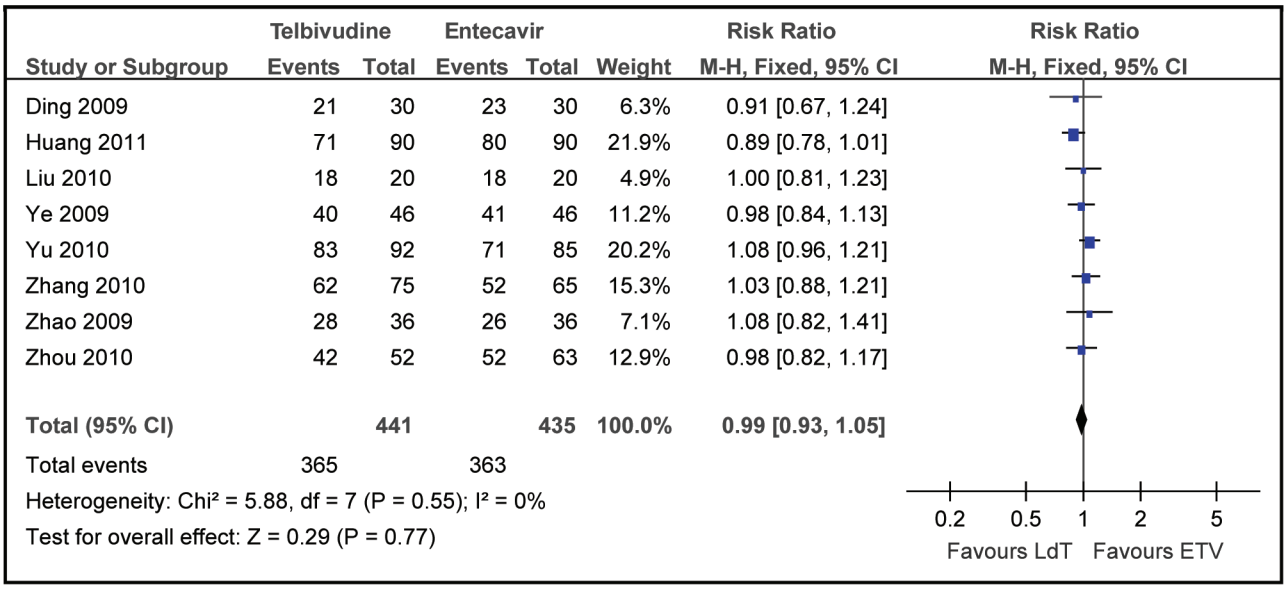

Figure 6. Forest plot of the 48-week virological response of LdT vs. ETV.

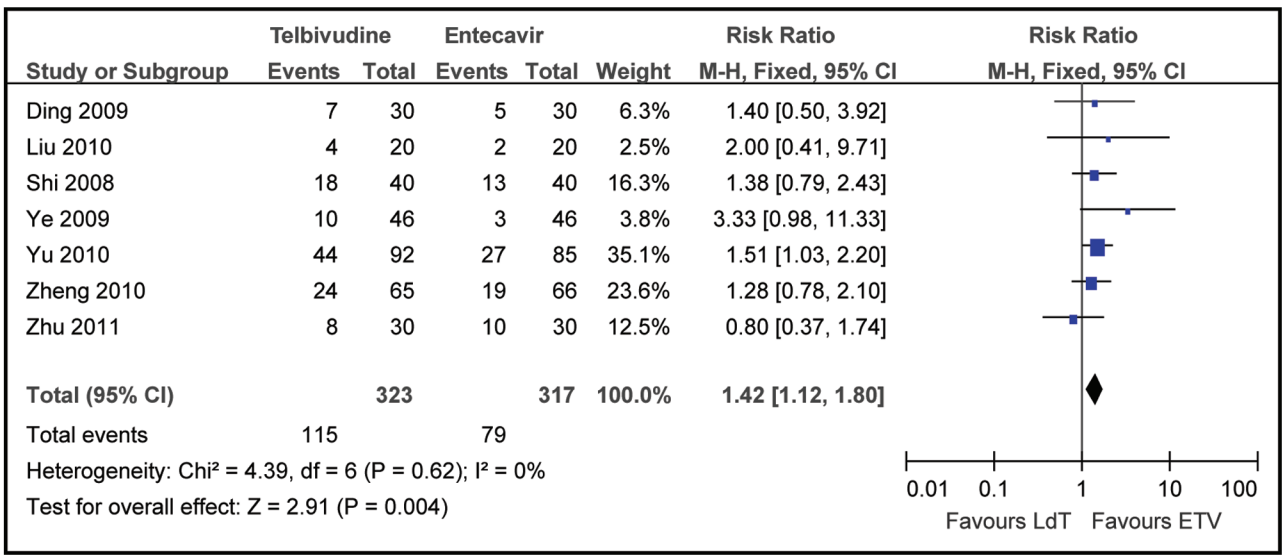

Figure 7. Forest plot of the 24-week HBeAg loss of LdT vs. ETV.

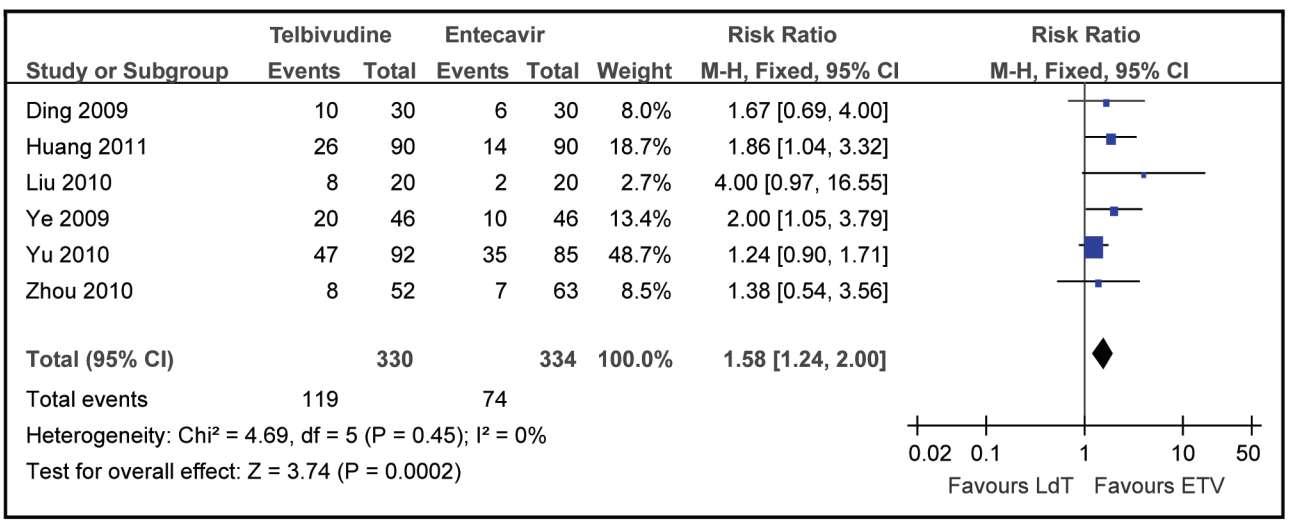

Figure 8. Forest plot of the 48-week HBeAg loss of LdT vs. ETV.

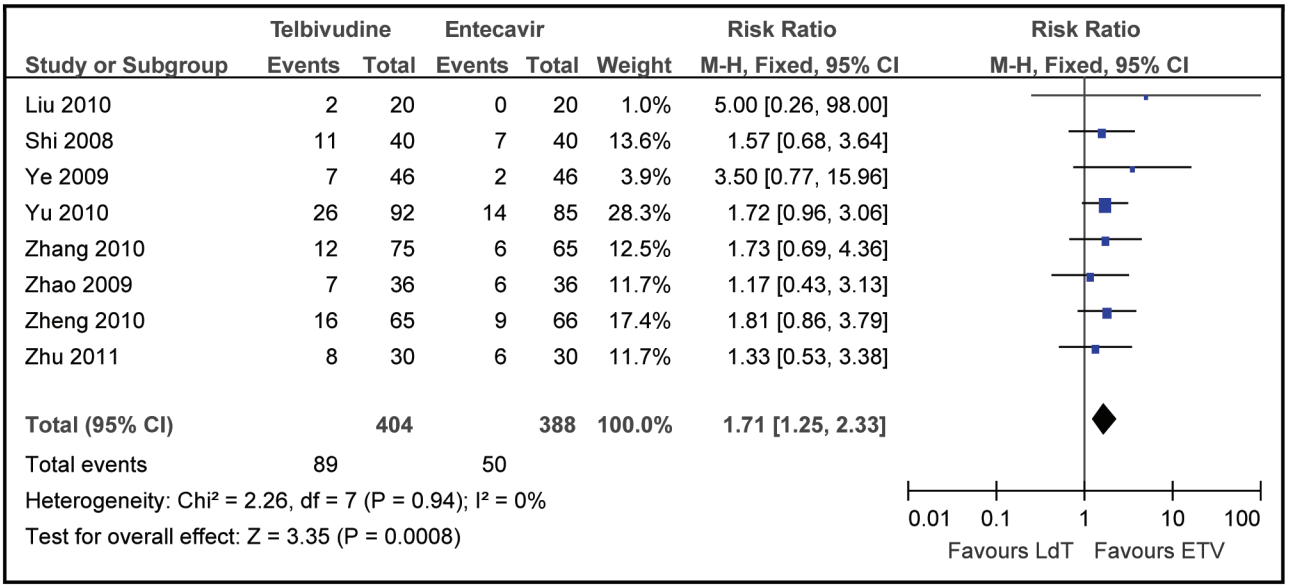

Figure 9. Forest plot of the 24-week HBeAg seroconversion of LdT vs. ETV.

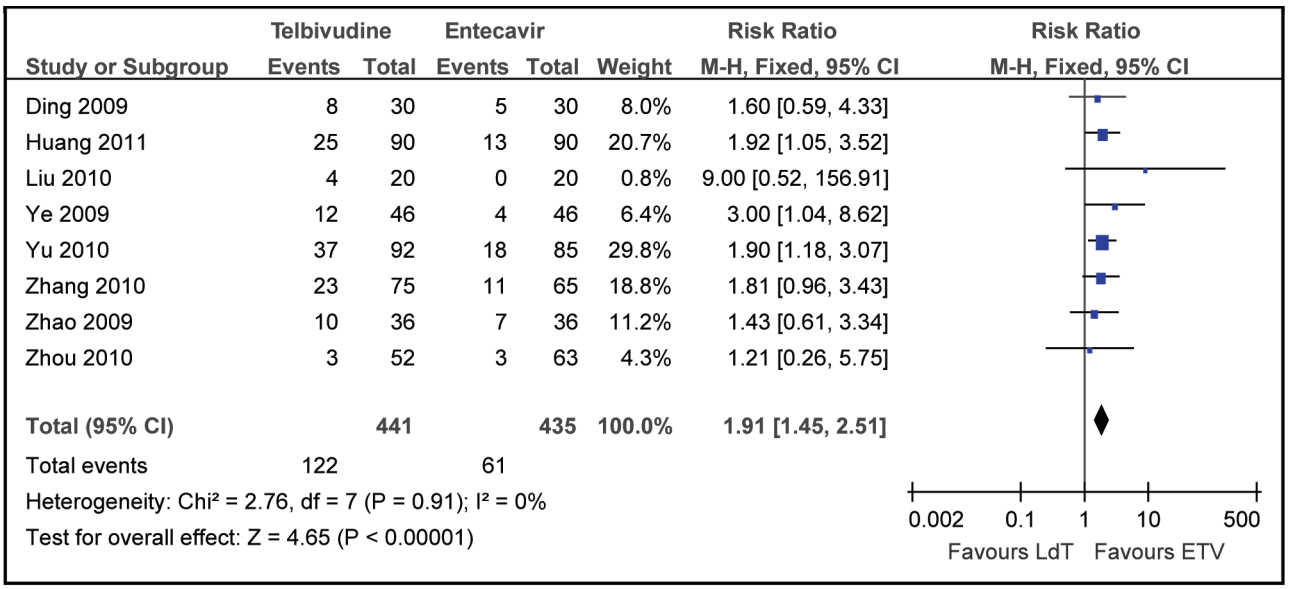

Figure 10. Forest plot of the 48-week HBeAg seroconversion of LdT vs. ETV.

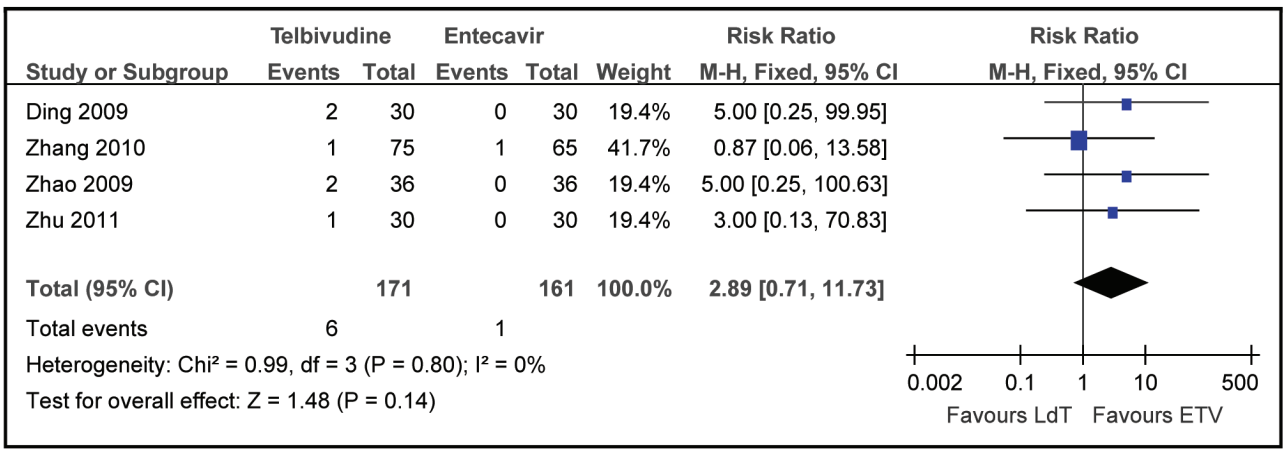

Figure 11. Forest plot of the drug resistance rates of LdT vs. ETV.

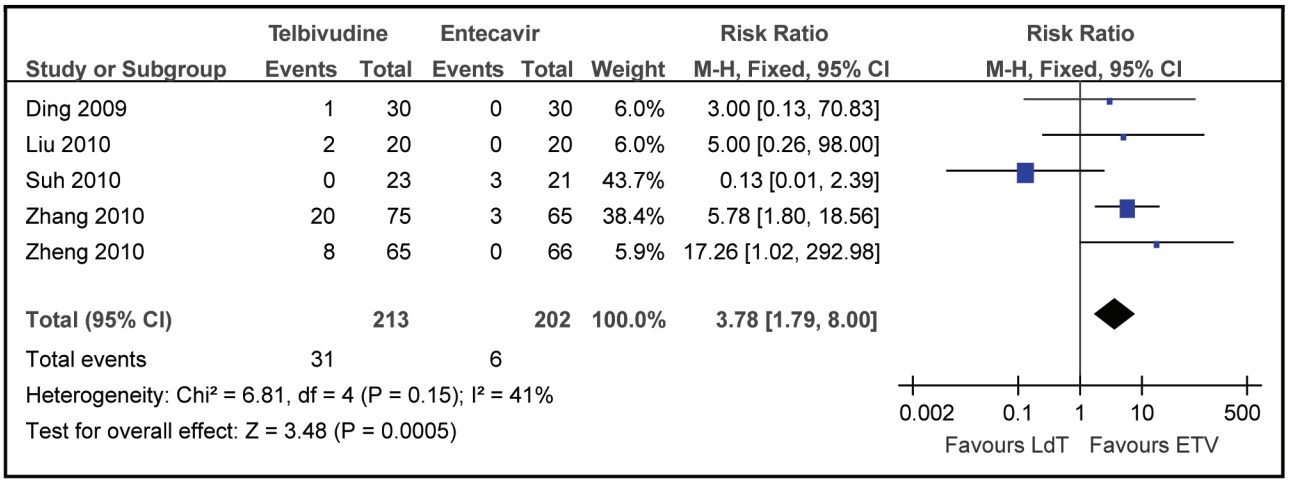

Figure 12. Forest plot of the CK elevation rates of LdT vs. ETV.

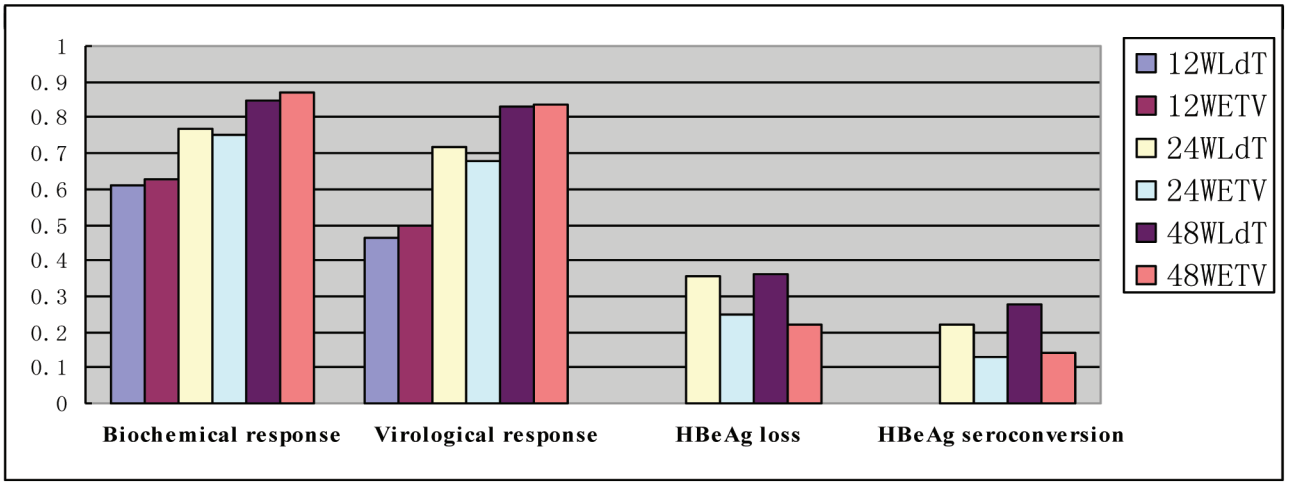

Figure 13. Comparison of biochemical response, virological response, HBeAg loss, and HBeAg seroconversion.

DISCUSSION

Treatment of chronic hepatitis B virus (HBV) infections has been revolutionized in the past decade by the increased availability of effective antiviral agents. LdT is an L-nucleoside that is structurally related to LAM, and recently has been approved for use in patients with chronic HBV infection. LdT is highly selective for HBV DNA and inhibits viral DNA synthesis with no effect on human DNA, or other viruses for that matter (32). The latest data has shown that three years of LdT treatment yielded high rates of viral suppression and ALT normalization with a favorable safety profile. High rates of HBeAg seroconversion were achieved with prolonged LdT therapy, and this was sustained in the majority of patients over 52 weeks of therapy (33). ETV is a carboxylic 2'-deoxyguanosine analog, and is approved in the US, EU, and many Asian countries (34). Although it was once considered to be one of the most potent agents widely used (35), the high costs limited its use in low-income areas. Ultimately, agents with good cost/benefit ratios will obviously be preferred options.

In this meta-analysis, we focused on clinical parameters including ALT normalization, HBV DNA suppression, HBeAg clearance, and HBeAg seroconversion to evaluate the efficacy between LdT and ETV treatments of CHB (Figure 11). The results revealed no significant difference in normalization of ALT and suppression of HBV DNA comparing LdT and ETV in short-term therapy. Our results were similar to those of previous reports (1,36,37). This study also revealed that LdT had greater efficacy than ETV for inducing HBeAg loss and HBeAg seroconversion at both 24 and 48 weeks. Treatment guidelines currently consider

HBeAg seroconversion to be an end point of treatment with oral antivirals for HBeAg-positive patients. However, recently, Fung et al. (38) reported on a high rate of HBV DNA rebound despite sustained HBeAg seroconversion in patients who discontinued lamivudine therapy. Frenette et al. (39) discovered that HBeAg status is not able to be used as a marker for prognosis, or treatment initiation or cessation. However, HBeAg status continued to be considered as a very important end point in HBV management (1,40). If patients with pre-core/core or basal core promoter region mutations are not counted, patients who achieved true HBeAg seroconversion combined with undetectable HBV DNA achieved better clinical outcomes with a continuous treatment of antiviral medications. However, antiviral drug resistance is a critical factor in determining the success of long-term therapy for chronic hepatitis B (9,41-43). The development of resistance to nucleoside analogs has been associated with exacerbation of liver disease. Therefore, more attention should be paid to the safety of these two drugs. Our study has indicated no significant difference in drug resistance between the two drugs in short-term therapy. Creatine kinase elevations were found to occur more frequently when utilizing LdT treatment.

There are limitations to this meta-analysis. First, the inclusive trials were not double-blinded. This deficiency could have affected the assessed outcomes. Second, not all of the included trials were randomized case-control studies. There was one trial included that was a cohort study. Next, we included trials only published in English and Chinese, and therefore we may have possibly introduced a language bias.

In conclusion, LdT is as potent as ETV in normalizing ALT and suppressing HBV DNA in short-term therapy. Also, LdT is superior to ETV in clearing HBeAg and developing anti-HBe in nuceos(t)ide-naïve Asian patients with HBeAg-positive CHB. Careful monitoring is needed to avoid side effects as well as monitoring for drug resistance during the antiviral therapy with LdT. Careful evaluation of the patient's history, staging of liver disease, and virological factors should guide the start of treatment, and will guide to the selection of the most appropriate individualized treatment strategy in all CHB patients.

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