Effects of telbivudine and entecavir for HBeAg-positive chronic hepatitis B: A meta-analysis

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Abstract

AIM: To compare the effects of telbivudine (LDT) and entecavir (ETV) in treatment of hepatitis B e antigen (HBeAg)-positive chronic hepatitis B by meta-analysis.

METHODS: We conducted a literature search using PubMed, MEDLINE, EMBASE, the China National Knowledge Infrastructure, the VIP database, the Wanfang database and the Cochrane Controlled Trial Register for all relevant articles published before April 1, 2012. Randomized controlled trials (RCTs) comparing LDT with ETV for treatment of HBeAg-positive chronic hepatitis B were included. The data was analyzed with Review Manager Software 5.0. We used relative risk (RR) as an effect measure, and reported its 95% CI. Meta-analysis was performed using either a fixed-effect or random-effect model, based on the absence or presence of significant heterogeneity. Two reviewers assessed the risk of bias and extracted data independently and in duplicate. The analysis was executed using the main outcome parameters including hepatitis B virus (HBV) DNA undetectability, alanine aminotransferase (ALT) normalization, HBeAg loss, HBeAg seroconversion, drug-resistance, and adverse reactions. Meta-analysis of the included trials and subgroup analyses were conducted to examine the association between pre-specified characteristics with the therapeutic effects of the two agents.

RESULTS: Thirteen eligible trials (3925 patients in total) were included and evaluated for methodological quality and heterogeneity. In various treatment durations of 4 wk, 8 wk, 12 wk, 24 wk, 36 wk, 48 wk, 52 wk, 60 wk and 72 wk, the rates of HBV DNA undetectability and ALT normalization in the two groups were similar, without statistical significance. At 4 wk and 8 wk of the treatment, no statistical differences were found in the rate of HBeAg loss between the two groups, while the rate in the LDT group was higher than in the ETV group at 12 wk, 24 wk, 48 wk and 52 wk, respectively (RR 2.28, 95% CI 1.16, 7.03, P = 0.02; RR 1.45, 95% CI 1.16, 1.82, P = 0.001; RR 1.45, 95% CI 1.11, 1.89, P = 0.006; and RR 1.86, 95% CI 1.04, 3.32, P = 0.04). At 4 wk, 8 wk, 60 wk and 72 wk of the treatment, there were no significant differences in the rate of HBeAg seroconversion between the two groups, while at 12 wk, 24 wk, 48 wk and 52 wk, the rate in the LDT group was higher than in the ETV group (RR 2.10, 95% CI 1.36, 3.24, P = 0.0008; RR 1.71, 95% CI 1.29, 2.28, P = 0.0002; RR 1.86, 95% CI 1.36, 2.54, P < 0.0001; and RR 1.87, 95% CI 1.21, 2.90, P = 0.005). The rate of drug-resistance was higher in the LDT group than in the ETV group (RR 3.76, 95% CI 1.28, 11.01, P = 0.02). In addition, no severe adverse drug reactions were observed in the two groups. And the rate of increased creatine kinase in the LDT group was higher than in the ETV group (RR 5.58, 95% CI 2.22, 13.98, P = 0.0002).

CONCLUSION: LDT and ETV have similar virological and biomedical responses, and both are safe and well tolerated. However, LDT has better serological response and higher drug-resistance.
We searched PubMed, MEDLINE, EMBASE, China MATERIALS AND METHODS

**Key words:** Telbivudine; Entecavir; Hepatitis B e antigen-positive chronic hepatitis B; Randomized controlled trials; Meta-analysis

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**INTRODUCTION**

Chronic hepatitis B (CHB) infection is a major health problem affecting over 350 million people worldwide.[1,2] CHB can lead to various life-threatening conditions, such as liver failure, liver cirrhosis (LC) and hepatocellular carcinoma (HCC).[3] Hepatitis B virus (HBV) covalent closed circular DNA (cccDNA) is the main cause of the sustainability of the hepatitis virus, and it is difficult to completely eliminate it.[4] So the primary therapeutic goal is to sustain viral suppression. Current anti-viral medication includes interferon [interferon-alpha (IFN-α), and pegylated (PEG) IFN-α] and nucleosides or nucleoside analogues [entecavir (ETV), adefovir dipivoxil, telbivudine (LDT), and lamivudine (L)].[5] Recent studies have shown that LDT and ETV are the strongest nucleoside analogues. LDT (β-L-2′-deoxynucleoside) is an orally bioavailable L-nucleoside. It can effectively suppress HBV DNA replication, and has a higher rate of hepatitis B e antigen (HBeAg) seroconversion than other current oral antiviral agents.[6] However, its drug-resistance remains high.[7] ETV is a new generation nucleoside analogues. It has the advantage of higher rate of HBV DNA suppression, low drug-resistance and high safety, especially in lamivudine-resistant CHB patients.[8] But the rates of HBeAg loss and seroconversion are very low in ETV group, which is difficult to meet the withdrawal standards. There are few systematic reviews about the comparison of LDT and ETV. Therefore, we conducted a meta-analysis of the randomized controlled trials (RCTs) using the Cochrane methodology to explore the efficacy of LDT and ETV for clinical treatment of HBeAg-positive chronic hepatitis B.

**RESULTS**

National Knowledge Infrastructure, the VIP database, the Wanfang database and the Cochrane Controlled Trial Register for articles published up to April 1, 2012, using the following keywords: “HBeAg-positive chronic hepatitis B”, “telbivudine”, “entecavir”, and “RCTs”. The reference lists of eligible studies were also searched.

**Inclusion criteria**

The following inclusion criteria were used: (1) RCTs; (2) Articles studying HBeAg-positive chronic hepatitis B patients, according to diagnostic standards in “China guidelines for HBV management (2010)”[9]; (3) Studies comparing LDT (600 mg/d) with ETV (0.5 mg/d); and (4) The main outcome parameters included virological, biochemical, and serological responses [HBV DNA undetectability, alanine aminotransferase (ALT) normalization, HBeAg loss, HBeAg seroconversion, drug-resistance, and adverse reactions]. Virological response was defined as attainment of undetectable levels of HBV DNA. Determined by quantitative polymerase chain reaction, the threshold of detection was 1000 copies/mL or less in each corresponding study (Table 1). Biochemical response was defined as normalization of ALT levels to below the upper limit of normal (< 40 IU/mL). HBeAg loss was defined as HBeAg levels < 1.0 S/CO, HBeAg seroconversion was defined as HBeAg loss and the presence of anti-HBeAg, determined by microparticle enzyme immunoassay or enzyme-linked immunosorbent assay.

**Exclusion criteria**

The following exclusion criteria were used: (1) Nonrandomized controlled trials (NRCTs); (2) Insufficient analytical information regarding treatment schedule, follow-up, and outcomes; (3) Patients receiving interferon, nucleosides or nucleotides for CHB within 6 mo; (4) Patients coinfected with hepatitis A, C, D and E virus, cytomegalovirus, or human immunodeficiency virus; (5) Patients with liver failure, HCC, and liver-related complications caused by alcoholism, autoimmune disease, and cholestasis; and (6) Pregnant and breastfeeding patients.

**Data extraction**

Data extraction was assessed independently by two reviewers (Song LY and Zhang SR). Discrepancies were solved through discussions between the reviewers or by a third person. Systematic Reviews of Interventions Version 5.0.2 (Cochrane Collaboration, Oxford, United Kingdom) was used to assess risk of bias (adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective reporting and free of other bias).[10] Basic information obtained from each eligible trial included study design, patient characteristics, number of two groups, treatment duration and related study results. Data were reviewed to eliminate duplicate reports of the same trial.

**Statistical analysis**

We used Review Manager Software 5.0 (Cochrane Collab-
oration, Oxford, United Kingdom) for the data analysis. For dichotomous data, we used relative risk (RR) as an effect measure, and reported its 95% CI. Meta-analysis was performed using either a fixed-effect or random-effect model, based on the absence or presence of significant heterogeneity.

Statistical heterogeneity between trials was evaluated by $\chi^2$ and $I^2$ analysis. The fixed-effect method was used in the absence of statistically significant heterogeneity ($P \geq 0.1$), and the random-effect method was used when the heterogeneity test was statistically significant ($P < 0.1$). $P < 0.05$ was regarded as statistically significant. Subgroup analysis was performed to examine the association between pre-specified characteristics (treatment duration) and the therapeutic effect, sensitivity analysis was made to estimate result stability, and funnel plots were used to assess publication bias if more than five trials were included[11].

RESULTS

Characteristics and quality of studies

We initially identified 1165 abstracts, and after evaluating the full texts, we included 13 trials (12 in Chinese and one in English)[12-24] based on the pre-specified criteria. A total of 3925 patients were included: 1987 treated with LDT and 1938 treated with ETV. Table 1 shows the characteristics of the 13 trials. All these studies showed baseline comparability, 9 of them reported the baseline of two groups in detail[13-15,17,19,20,22-24], the other 4 presented no significant differences in gender, age and duration of treatment between the two groups[12,16,18,21]. Three described the methods of randomization in detail[13,14,24], nine reported randomization, but did not describe the method of randomization in detail[12,15,17-23], one reported allocation concealment[24] and two presented blinding method[22,24]. None of the trials referred to incomplete outcome data addressed, free of selective reporting, and free of other bias. Various risks of bias in the 13 trials. In addition, none of the trials reported mortality, life quality and liver cancer incidence are shown in Figure 1.

HBV DNA undetectability

All the trials reported the rate of HBV DNA undetectability. $\chi^2$ and $I^2$ analyses showed no heterogeneity ($\chi^2 = 35.37, P = 0.74, I^2 = 0\%$); therefore, we used the fixed-effect method to analyze the data. The results showed that in various treatment durations of 4 wk, 8 wk, 12 wk, 24 wk, 36 wk, 48 wk, 52 wk, 60 wk and 72 wk, there were no statistical differences in the rate of HBV DNA undetectability between the two groups (RR 1.04, 95% CI 0.72, 1.49, $P = 0.85$; RR 0.98, 95% CI 0.74, 1.28, $P = 0.86$; RR 1.01, 95% CI 0.89, 1.15, $P = 0.83$; RR 1.06, 95% CI 0.99, 1.14, $P = 0.12$; RR 1.03, 95% CI 0.86, 1.37, $P = 1.24$; RR 1.02, 95% CI 0.95, 1.09, $P = 0.63$; RR 0.95, 95% CI 0.86, 1.05, $P = 0.29$; RR 1.02, 95% CI 0.83, 1.24, $P = 0.88$; and RR 0.95, 95% CI 0.80, 1.12, $P = 0.54$) (Figure 2A).

ALT normalization

Eleven trials reported the rate of ALT normalization[12,15,17,20,22,24]. $\chi^2$ and $I^2$ analyses showed no heterogeneity ($\chi^2 = 32.22, P = 0.51, I^2 = 0\%$). At various treatment durations of 4 wk, 8 wk, 12 wk, 24 wk, 36 wk, 48 wk, 52 wk, 60 wk and 72 wk, there were no statistical differences in the rate of ALT normalization between the two groups (RR 1.08, 95% CI 0.81, 1.43, $P = 0.59$; RR 1.05, 95% CI 0.77, 1.43, $P = 0.77$; 0.95, 95% CI 0.80, 1.12, $P = 0.54$).
RR 1.05, 95% CI 0.94, 1.16, P = 0.40; RR 1.00, 95% CI 0.93, 1.08, P = 0.91; RR 0.95, 95% CI 0.67, 1.34, P = 0.78; RR 1.01, 95% CI 0.92, 1.11, P = 1.08; RR 0.94, 95% CI 0.86, 1.02, P = 0.14; RR 0.96, 95% CI 0.77, 1.19, P = 0.69; and RR 0.98, 95% CI 0.84, 1.13, P = 0.76 (Figure 2B).

**HBeAg loss**

Ten trials reported the rate of HBeAg loss\(^{[13-16,18,20-24]}\) and \(I^2\) analyses found no heterogeneity (\(\chi^2 = 38.84, P = 0.04\), \(I^2 = 36\%\)). At 4 wk and 8 wk of the treatment, no statistical differences in the rate of HBeAg loss were observed between the two groups (RR 2.89, 95% CI 0.31, 27.23, \(P = 0.35\); and RR 1.50, 95% CI 0.50, 4.46, \(P = 0.47\)). At 12 wk, 24 wk, 48 wk and 52 wk, the rate of HBeAg loss was higher in the LDT group than in the ETV group, and the difference between two groups was statistically significant (RR 2.28, 95% CI 1.16, 7.03, \(P = 0.02\); RR 1.45, 95% CI 1.16, 1.82, \(P = 0.001\); RR 1.45, 95% CI 1.11, 1.89, \(P = 0.006\); RR 1.86, 95% CI 1.04, 3.32, \(P = 0.04\)) (Figure 2C).

**HBeAg seroconversion**

All the trials reported the rate of HBeAg seroconversion. \(\chi^2\) and \(I^2\) analyses showed no heterogeneity (\(\chi^2 = 22.15, P = 0.85, I^2 = 0\%\)). At 4 wk, 8 wk, 60 wk and 72 wk of the treatment, the rate of HBeAg seroconversion in the two groups was similar, and no statistically significant differences were observed (RR 2.34, 95% CI 0.55, 9.92, \(P = 0.25\); RR 1.55, 95% CI 0.77, 3.12, \(P = 0.22\); RR 1.56, 95% CI 0.91, 2.67, \(P = 0.1\)). However, at 12 wk, 24 wk, 48 wk and 52 wk, the rate of HBeAg loss was higher in the LDT group than in the ETV group, with statistically significant difference between two groups (RR 2.1, 95% CI 1.36, 3.24, \(P = 0.0008\); RR 1.71, 95% CI 1.29, 2.28, \(P = 0.0002\); RR 1.86, 95% CI 1.36, 2.54, \(P < 0.0001\); RR 1.87, 95% CI 1.21, 2.90, \(P = 0.005\)) (Figure 2D).

**Drug-resistance**

Six trials reported drug-resistance\(^{[12-13,16,17,22,23]}\). \(\chi^2\) and \(I^2\) analyses showed no heterogeneity (\(\chi^2 = 0.63, P = 0.96\), \(I^2 = 0\%\)). The rate of drug-resistance was higher in the LDT group than in the ETV group, and the difference between two groups was statistically significant (RR = 3.76, 95% CI 1.28, 11.01, \(P = 0.02\)) (Figure 2E).

### Adverse reactions

Ten trials reported on the adverse reactions\(^{[12-18,20,23,24]}\). No severe adverse reactions were observed in both groups. Common adverse reactions in the two groups included influenza-like symptoms such as fever, headache, fatigue, muscular stiffness, gastrointestinal upset such as nausea and diarrhea, alopecia and rash. Five of the trials reported the rate of increased creatine kinase (CK)\(^{[10,17,18,23,24]}\). \(\chi^2\) and \(I^2\) analyses showed no heterogeneity (\(\chi^2 = 1.06, P = 0.94, I^2 = 0\%\)). The rate of increased CK was higher in the LDT group than in the ETV group, the difference being statistically significant (RR 5.58, 95% CI 2.22, 13.98, \(P = 0.0002\)). But the increased CK recovered without any intervention, and did not influence the anti-HBV treatment (Figure 2F).

### Statistical analysis

Meta-analysis was performed based on the rate of HBeAg seroconversion, using the fixed-effect model, and the minimum sample size trials were excluded\(^{[18]}\). Odds ratio (OR) of all sensitivity analyses was higher than 1 and statistically significant (\(P < 0.05\)) (Table 2).

### Funnel plots

Funnel plots were performed based on the rate of HBV DNA undetectability. The results showed that funnel plots were symmetric and suggested that there was no publication bias (Figure 3).

### DISCUSSION

The RCTs comparing LDT with ETV for patients with HBeAg-positive chronic hepatitis B were included, and meta-analyses on virology, serology, biochemical respons-
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| A | Study of subgroup | LDT | ETV | Risk ratio | Risk ratio |
|---|------------------|-----|-----|------------|------------|
|   | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 1.1.1 4 wk |   |       |       |       |       |            |            |
| Ding et al | 9 | 30 | 8 | 30 | 0.6% | 1.13 [0.50, 2.52] |   |
| Yu et al | 2 | 92 | 1 | 85 | 0.1% | 1.85 [0.17, 20.01] |   |
| Liu et al | 15 | 20 | 16 | 20 | 1.3% | 0.94 [0.67, 1.31] |   |
| Subtotal (95% CI) | 142 | 135 | 2.0% | 1.04 [0.72, 1.49] |   |
| Total events | 26 | 25 |   |   |   |            |            |
| Heterogeneity: $\chi^2 = 0.61, df = 2 (P = 0.74); I^2 = 0\%$ |   |   |   |   |   |            |            |
| Test for overall effect: $Z = 0.19 (P = 0.85)$ |   |   |   |   |   |            |            |
| 1.1.2 8 wk |   |       |       |       |       |            |            |
| Zhang et al | 16 | 75 | 20 | 65 | 1.7% | 0.69 [0.39, 1.22] |   |
| Ding et al | 12 | 30 | 11 | 30 | 0.9% | 1.09 [0.57, 2.07] |   |
| Zhao et al | 9 | 42 | 12 | 39 | 1.0% | 0.70 [0.33, 1.47] |   |
| Yu et al | 35 | 92 | 25 | 85 | 2.0% | 1.29 [0.85, 1.97] |   |
| Subtotal (95% CI) | 239 | 219 | 5.5% | 0.98 [0.74, 1.28] |   |
| Total events | 72 | 68 |   |   |   |            |            |
| Heterogeneity: $\chi^2 = 4.02, df = 3 (P = 0.26); I^2 = 25\%$ |   |   |   |   |   |            |            |
| Test for overall effect: $Z = 0.18 (P = 0.86)$ |   |   |   |   |   |            |            |
| 1.1.3 12 wk |   |       |       |       |       |            |            |
| Zhu et al | 11 | 30 | 23 | 30 | 1.8% | 0.48 [0.29, 0.80] |   |
| Xu et al | 21 | 30 | 17 | 30 | 1.3% | 1.24 [0.84, 1.83] |   |
| Zhang et al | 34 | 75 | 34 | 65 | 2.9% | 0.87 [0.62, 1.22] |   |
| Ding et al | 15 | 30 | 15 | 30 | 1.2% | 1.00 [0.60, 1.66] |   |
| Shi et al | 20 | 40 | 20 | 40 | 1.6% | 1.00 [0.65, 1.55] |   |
| Zhao et al | 19 | 42 | 20 | 39 | 1.6% | 0.98 [0.56, 1.39] |   |
| Zheng et al | 28 | 65 | 23 | 66 | 1.8% | 1.24 [0.80, 1.90] |   |
| Yu et al | 45 | 92 | 40 | 85 | 3.3% | 1.04 [0.76, 1.41] |   |
| Ye et al | 24 | 46 | 15 | 46 | 1.2% | 1.60 [0.97, 2.64] |   |
| Liu et al | 17 | 20 | 17 | 20 | 1.3% | 1.00 [0.77, 1.30] |   |
| Zhou et al | 23 | 52 | 25 | 63 | 1.8% | 1.11 [0.72, 1.72] |   |
| Subtotal (95% CI) | 522 | 514 | 19.7% | 1.01 [0.90, 1.15] |   |
| Total events | 257 | 249 |   |   |   |            |            |
| Heterogeneity: $\chi^2 = 14.74, df = 10 (P = 0.14); I^2 = 32\%$ |   |   |   |   |   |            |            |
| Test for overall effect: $Z = 0.21 (P = 0.83)$ |   |   |   |   |   |            |            |
| 1.1.4 24 wk |   |       |       |       |       |            |            |
| Zhu et al | 18 | 30 | 21 | 30 | 1.6% | 0.86 [0.59, 1.25] |   |
| Xu et al | 26 | 30 | 22 | 30 | 1.7% | 1.18 [0.91, 1.53] |   |
| Zhao et al | 26 | 30 | 24 | 30 | 1.9% | 1.08 [0.86, 1.36] |   |
| Zhang et al | 51 | 75 | 43 | 65 | 3.6% | 1.03 [0.81, 1.30] |   |
| Ding et al | 17 | 30 | 21 | 30 | 1.6% | 0.81 [0.55, 1.20] |   |
| Shi et al | 32 | 40 | 28 | 40 | 2.2% | 1.14 [0.89, 1.48] |   |
| Zhao et al | 29 | 42 | 26 | 42 | 2.0% | 1.12 [0.82, 1.52] |   |
| Zheng et al | 44 | 65 | 38 | 66 | 3.0% | 1.18 [0.90, 1.53] |   |
| Yu et al | 72 | 92 | 57 | 85 | 4.6% | 1.17 [0.97, 1.40] |   |
| Ye et al | 33 | 46 | 34 | 48 | 2.6% | 1.01 [0.78, 1.31] |   |
| Liu et al | 17 | 20 | 17 | 20 | 1.3% | 1.00 [0.77, 1.30] |   |
| Zhou et al | 42 | 52 | 52 | 63 | 3.7% | 0.98 [0.82, 1.17] |   |
| Subtotal (95% CI) | 552 | 549 | 29.9% | 1.06 [0.99, 1.14] |   |
| Total events | 407 | 383 |   |   |   |            |            |
| Heterogeneity: $\chi^2 = 7.04, df = 11 (P = 0.80); I^2 = 0\%$ |   |   |   |   |   |            |            |
| Test for overall effect: $Z = 1.57 (P = 0.12)$ |   |   |   |   |   |            |            |
| 1.1.5 36 wk |   |       |       |       |       |            |            |
| Ding et al | 20 | 30 | 22 | 30 | 1.7% | 0.91 [0.65, 1.27] |   |
| Zhou et al | 40 | 52 | 44 | 63 | 3.1% | 1.10 [0.88, 1.37] |   |
| Subtotal (95% CI) | 82 | 93 | 4.8% | 1.03 [0.86, 1.24] |   |
| Total events | 60 | 66 |   |   |   |            |            |
| Heterogeneity: $\chi^2 = 0.89, df = 1 (P = 0.34); I^2 = 0\%$ |   |   |   |   |   |            |            |
| Test for overall effect: $Z = 0.35 (P = 0.73)$ |   |   |   |   |   |            |            |
| 1.1.6 48 wk |   |       |       |       |       |            |            |
| Zhao et al | 28 | 36 | 26 | 36 | 2.0% | 1.08 [0.82, 1.41] |   |
| Ding et al | 21 | 30 | 23 | 30 | 1.8% | 0.91 [0.67, 1.24] |   |
| Zhao et al | 34 | 42 | 31 | 39 | 2.5% | 1.02 [0.82, 1.26] |   |
| Yu et al | 83 | 92 | 71 | 85 | 5.8% | 1.08 [0.96, 1.21] |   |
| Ye et al | 40 | 46 | 41 | 46 | 3.2% | 0.98 [0.84, 1.13] |   |
| Liu et al | 18 | 20 | 18 | 20 | 1.4% | 1.00 [0.81, 1.23] |   |
| Zhou et al | 42 | 52 | 52 | 63 | 3.7% | 0.98 [0.82, 1.17] |   |
Subtotal (95% CI) 318 319 20.4% 1.02 [0.95, 1.09]
Total events 266 262
Heterogeneity: $\chi^2 = 2.19$, df = 6 ($P = 0.90$); $I^2 = 0$
Test for overall effect: $Z = 0.48$ ($P = 0.63$)

1.1.7 52 wk
Huang et al 71 90 80 90 6.3% 0.89 [0.78, 1.01]
Zhang et al 62 75 52 65 4.4% 1.03 [0.88, 1.21]
Subtotal (95% CI) 165 155 10.6% 0.95 [0.86, 1.05]
Total events 133 132
Heterogeneity: $\chi^2 = 2.11$, df = 1 ($P = 0.15$); $I^2 = 53$
Test for overall effect: $Z = 1.05$ ($P = 0.29$)

1.1.8 60 wk
Zhao et al 35 42 32 39 2.6% 1.02 [0.83, 1.24]
Subtotal (95% CI) 42 39 2.6% 1.02 [0.83, 1.24]
Total events 35 32
Heterogeneity: Not applicable
Test for overall effect: $Z = 0.15$ ($P = 0.88$)

1.1.9 72 wk
Zhang et al 58 75 53 65 4.4% 0.95 [0.80, 1.12]
Subtotal (95% CI) 75 65 4.4% 0.95 [0.80, 1.12]
Total events 58 53
Heterogeneity: Not applicable
Test for overall effect: $Z = 0.62$ ($P = 0.54$)

Total (95% CI) 2137 2088 100.0% 1.02 [0.98, 1.06]
Total events 1314 1270
Heterogeneity: $\chi^2 = 35.78$, df = 42 ($P = 0.74$); $I^2 = 0$

1.2.1 4 wk
Ding et al 8 30 7 30 0.7% 1.14 [0.47, 2.75]
Liu et al 19 20 18 20 1.8% 1.06 [0.88, 1.26]
Subtotal (95% CI) 50 50 2.5% 1.08 [0.81, 1.43]
Total events 27 25
Heterogeneity: $\chi^2 = 0.08$, df = 1 ($P = 0.78$); $I^2 = 0$
Test for overall effect: $Z = 0.53$ ($P = 0.59$)

1.2.2 8 wk
Zhang et al 27 75 23 65 2.4% 1.02 [0.65, 1.59]
Ding et al 13 30 12 30 1.2% 1.08 [0.59, 1.97]
Zhao et al 15 42 13 39 1.3% 1.07 [0.59, 1.95]
Subtotal (95% CI) 147 134 4.9% 1.05 [0.77, 1.43]
Total events 55 48
Heterogeneity: $\chi^2 = 0.03$, df = 2 ($P = 0.98$); $I^2 = 0$
Test for overall effect: $Z = 0.30$ ($P = 0.77$)

1.2.3 12 wk
Zhao et al 16 30 22 30 2.0% 0.73 [0.49, 1.08]
Xu et al 15 30 18 30 1.8% 0.83 [0.53, 1.32]
Zhang et al 56 75 43 65 4.5% 1.13 [0.91, 1.40]
Ding et al 15 30 16 30 1.6% 0.94 [0.57, 1.53]
Shi et al 21 40 24 40 2.4% 0.88 [0.59, 1.29]
Zhao et al 30 42 27 39 2.7% 1.03 [0.78, 1.37]
Zheng et al 56 65 38 65 3.7% 1.47 [1.17, 1.85]
Ye et al 23 46 25 46 2.5% 0.92 [0.62, 1.36]
Liu et al 19 20 18 20 1.8% 1.06 [0.88, 1.26]
Subtotal (95% CI) 378 365 23.0% 1.05 [0.94, 1.16]
Total events 251 231
Heterogeneity: $\chi^2 = 14.80$, df = 8 ($P = 0.06$); $I^2 = 46$
Test for overall effect: $Z = 0.84$ ($P = 0.40$)

1.2.4 24 wk
Zhao et al 22 30 27 30 2.6% 0.81 [0.64, 1.04]
Xu et al 23 30 27 30 2.6% 0.85 [0.68, 1.07]
Zhao et al 28 36 26 36 2.5% 1.08 [0.82, 1.41]
Zhang et al 57 75 44 65 4.6% 1.12 [0.91, 1.39]
Ding et al 16 30 18 30 1.8% 0.89 [0.57, 1.39]
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Shi et al  31  40  30  40  2.9%  1.03 [0.81, 1.32]
Zhao et al  32  42  29  39  2.9%  1.02 [0.80, 1.32]
Zheng et al  51  65  49  66  4.8%  1.06 [0.87, 1.28]
Ye et al  39  46  40  46  3.9%  0.97 [0.83, 1.15]
Liu et al  18  20  17  20  1.7%  1.06 [0.84, 1.34]
Subtotal (95% CI)  414  402  30.5%  1.00 [0.93, 1.08]

Total events  317  307
Heterogeneity: $\chi^2 = 7.01$, df = 9 ($P = 0.64$); $I^2 = 0$
Test for overall effect: $Z = 0.11$ ($P = 0.91$)

Zhao et al  32  42  29  39  2.9%  1.02 [0.80, 1.32]
Zheng et al  51  65  49  66  4.8%  1.06 [0.87, 1.28]
Ye et al  39  46  40  46  3.9%  0.97 [0.83, 1.15]
Liu et al  18  20  17  20  1.7%  1.06 [0.84, 1.34]
Subtotal (95% CI)  414  402  30.5%  1.00 [0.93, 1.08]

Total events  317  307
Heterogeneity: $\chi^2 = 7.01$, df = 9 ($P = 0.64$); $I^2 = 0$
Test for overall effect: $Z = 0.11$ ($P = 0.91$)

Zheng et al  51  65  49  66  4.8%  1.06 [0.87, 1.28]
Ye et al  39  46  40  46  3.9%  0.97 [0.83, 1.15]
Liu et al  18  20  17  20  1.7%  1.06 [0.84, 1.34]
Subtotal (95% CI)  414  402  30.5%  1.00 [0.93, 1.08]

Total events  317  307
Heterogeneity: $\chi^2 = 7.01$, df = 9 ($P = 0.64$); $I^2 = 0$
Test for overall effect: $Z = 0.11$ ($P = 0.91$)

1.2.5 36 wk

Ding et al  20  30  21  30  2.1%  0.95 [0.67, 1.34]
Subtotal (95% CI)  30  30  2.1%  0.95 [0.67, 1.34]

Total events  20  21
Heterogeneity: Not applicable
Test for overall effect: $Z = 0.28$ ($P = 0.78$)

1.2.6 48 wk

Zhao et al  30  36  28  36  2.7%  1.07 [0.85, 1.35]
Ding et al  23  30  24  30  2.4%  0.96 [0.73, 1.25]
Zhao et al  30  36  28  36  2.7%  1.07 [0.85, 1.35]
Ye et al  43  46  42  46  4.1%  1.02 [0.91, 1.15]
Liu et al  18  20  18  20  1.8%  1.00 [0.81, 1.23]
Subtotal (95% CI)  174  171  14.1%  1.01 [0.92, 1.11]

Total events  147  143
Heterogeneity: $\chi^2 = 0.50$, df = 4 ($P = 0.97$); $I^2 = 0$
Test for overall effect: $Z = 0.24$ ($P = 0.81$)

Huang et al  75  90  86  90  8.4%  0.87 [0.79, 0.97]
Zhang et al  62  75  52  65  5.5%  1.03 [0.88, 1.21]
Subtotal (95% CI)  137  138  13.9%  0.94 [0.86, 1.02]

Total events  137  138
Heterogeneity: $\chi^2 = 3.29$, df = 1 ($P = 0.07$); $I^2 = 70$
Test for overall effect: $Z = 1.46$ ($P = 0.14$)

1.2.8 60 wk

Zhao et al  33  42  32  39  3.3%  0.96 [0.77, 1.19]
Subtotal (95% CI)  42  39  3.3%  0.96 [0.77, 1.19]

Total events  33  32
Heterogeneity: Not applicable
Test for overall effect: $Z = 0.39$ ($P = 0.69$)

1.2.9 72 wk

Zhang et al  62  75  55  65  5.8%  0.98 [0.84, 1.13]
Subtotal (95% CI)  127  120  10.1%  0.98 [0.84, 1.13]

Total events  62  55
Heterogeneity: Not applicable
Test for overall effect: $Z = 0.31$ ($P = 0.76$)

Total (95% CI)  1475  1411  100.0%  1.01 [0.96, 1.05]

Total events  1049  1000
Heterogeneity: $\chi^2 = 32.22$, df = 33 ($P = 0.51$); $I^2 = 0$
Test for overall effect: $Z = 0.23$ ($P = 0.82$)

Test for subgroup differences: Not applicable.

| Study of subgroup | LDT Events | LDT Total | ETV Events | ETV Total | Weight | Risk ratio M-H, Random, 95% CI | Risk ratio M-H, Random, 95% CI |
|------------------|------------|-----------|------------|-----------|--------|-------------------------------|-------------------------------|
| 1.3.1 4 wk       |            |           |            |           |        |                               |                               |
| Ding et al       | 1          | 30        | 0          | 30        | 0.5%   | 3.00 [0.13, 70.83]            |                               |
| Yu et al         | 1          | 92        | 0          | 85        | 0.5%   | 2.77 [0.11, 67.19]            |                               |
| Liu et al        | 0          | 20        | 0          | 20        | Not estimable                  |                               |
| Subtotal (95% CI)| 142        | 135       | 0.9%       | 2.89 [0.31, 27.23]              |                               |
| Total events     | 2          | 0         |            |            |        |                               |                               |
| Heterogeneity:   | Tau$^2$ = 0.00; $\chi^2 = 0.00$, df = 1 ($P = 0.97$); $I^2 = 0$ |                               |                               |
| Test for overall effect: $Z = 0.93$ ($P = 0.35$) |                               |                               |

1.3.2 8 wk

Ding et al  2  30  1  30  0.8%  2.00 [0.19, 20.90]
Yu et al  6  92  4  85  2.6%  1.39 [0.40, 4.79]
Subtotal (95% CI)  122  115  3.4%  1.50 [0.50, 4.46]

Total events  8  5

Test for overall effect: $Z = 0.35$ ($P = 0.72$)

Test for subgroup differences: Not applicable.
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Heterogeneity: \( \tau^2 = 0.00; \chi^2 = 0.07, df = 1 (P = 0.79); I^2 = 0\%

Test for overall effect: \( Z = 0.73 (P = 0.47) \)

### 1.3.3 12 wk

| Study of subgroup | LDT | ETV | Total | Weight | Risk ratio M-H, Fixed, 95% CI |
|------------------|-----|-----|-------|--------|-----------------------------|
| Zhu et al        | 6   | 30  | 14    | 30     | 4.7% 0.43 [0.19, 0.96]       |
| Xu et al         | 11  | 30  | 5     | 30     | 4.0% 2.20 [0.87, 5.57]       |
| Ding et al       | 5   | 30  | 3     | 30     | 2.2% 1.67 [0.44, 6.36]       |
| Shi et al        | 12  | 40  | 2     | 40     | 2.0% 6.00 [1.43, 25.11]      |
| Zheng et al      | 13  | 65  | 2     | 66     | 2.0% 6.60 [1.55, 28.10]      |
| Yu et al         | 27  | 97  | 4     | 85     | 3.5% 5.91 [2.16, 16.22]      |
| Ye et al         | 3   | 46  | 0     | 46     | 0.5% 7.00 [0.37, 131.81]     |
| Liu et al        | 3   | 20  | 0     | 20     | 0.5% 7.00 [0.38, 127.32]     |
| Subtotal (95% CI)| 358 | 347 |       |        | 19.5% 2.86 [1.16, 7.03]      |

Total events 80

Heterogeneity: \( \tau^2 = 1.10; \chi^2 = 25.62, df = 7 (P = 0.0006); I^2 = 73\%

Test for overall effect: \( Z = 2.29 (P = 0.02) \)

### 1.3.4 24 wk

| Study of subgroup | LDT | ETV | Total | Weight | Risk ratio M-H, Fixed, 95% CI |
|------------------|-----|-----|-------|--------|-----------------------------|
| Zhu et al        | 8   | 30  | 10    | 30     | 5.0% 0.80 [0.37, 1.74]       |
| Xu et al         | 14  | 30  | 6     | 30     | 4.7% 2.33 [1.04, 5.25]       |
| Ding et al       | 7   | 30  | 5     | 30     | 3.4% 1.40 [0.50, 3.92]       |
| Shi et al        | 18  | 40  | 13    | 40     | 7.2% 1.38 [0.79, 2.43]       |
| Zheng et al      | 24  | 65  | 19    | 66     | 8.0% 1.28 [0.78, 2.10]       |
| Yu et al         | 44  | 92  | 27    | 85     | 9.7% 1.51 [1.03, 2.20]       |
| Ye et al         | 10  | 46  | 3     | 46     | 2.6% 3.33 [0.98, 11.33]      |
| Liu et al        | 4   | 20  | 2     | 20     | 1.7% 2.00 [0.41, 9.71]       |
| Subtotal (95% CI)| 353 | 347 |       |        | 42.3% 1.45 [1.16, 1.82]      |

Total events 129

Heterogeneity: \( \tau^2 = 0.00; \chi^2 = 5.83, df = 7 (P = 0.56); I^2 = 0\%

Test for overall effect: \( Z = 3.22 (P = 0.001) \)

### 1.3.6 48 wk

| Study of subgroup | LDT | ETV | Total | Weight | Risk ratio M-H, Fixed, 95% CI |
|------------------|-----|-----|-------|--------|-----------------------------|
| Ding et al       | 10  | 30  | 6     | 30     | 4.3% 1.67 [0.69, 4.00]       |
| Yu et al         | 47  | 92  | 35    | 85     | 10.5% 1.24 [0.90, 1.71]      |
| Ye et al         | 20  | 46  | 10    | 46     | 6.3% 2.00 [1.05, 3.79]       |
| Liu et al        | 8   | 20  | 2     | 20     | 2.0% 4.00 [0.97, 16.55]      |
| Zhou et al       | 8   | 52  | 7     | 63     | 3.8% 1.38 [0.54, 3.56]       |
| Subtotal (95% CI)| 240 | 244 |       |        | 27.0% 1.45 [1.11, 1.89]      |

Total events 93

Heterogeneity: \( \tau^2 = 0.00; \chi^2 = 4.06, df = 4 (P = 0.40); I^2 = 2\%

Test for overall effect: \( Z = 2.75 (P = 0.006) \)

### 1.3.7 52 wk

| Study of subgroup | LDT | ETV | Total | Weight | Risk ratio M-H, Fixed, 95% CI |
|------------------|-----|-----|-------|--------|-----------------------------|
| Huang et al      | 26  | 90  | 14    | 90     | 7.0% 1.86 [1.04, 3.32]       |
| Subtotal (95% CI)| 90  | 90  |       |        | 7.0% 1.86 [1.04, 3.32]       |

Total events 26

Heterogeneity: Not applicable

Test for overall effect: \( Z = 2.09 (P = 0.04) \)

Total (95% CI) 1305 1278 100.0% 1.68 [1.35, 2.09]

Total events 338 194

Heterogeneity: \( \tau^2 = 38.84, df = 25 (P = 0.04); I^2 = 36\%

Test for overall effect: \( Z = 4.66 (P < 0.00001) \)

### D

| Study of subgroup | LDT | ETV | Total | Weight | Risk ratio M-H, Fixed, 95% CI |
|------------------|-----|-----|-------|--------|-----------------------------|
| 1.4 4 wk         |     |     |       |        |                             |
| Yu et al         | 0   | 92  | 0     | 85     | Not estimable               |
| Liu et al        | 0   | 20  | 0     | 20     | Not estimable               |
| Subtotal (95% CI)| 112 | 105 |       |        | Not estimable               |

Total events 0

Heterogeneity: Not applicable

Test for overall effect: Not applicable

### 1.4 2 8 wk

| Study of subgroup | LDT | ETV | Total | Weight | Risk ratio M-H, Fixed, 95% CI |
|------------------|-----|-----|-------|--------|-----------------------------|
| Zhang et al      | 3   | 75  | 1     | 65     | 0.6% 2.60 [0.28, 24.39]      |
| Zhao et al       | 2   | 42  | 1     | 39     | 0.5% 1.86 [0.18, 19.68]      |
| Yu et al         | 1   | 92  | 0     | 85     | 0.3% 2.77 [0.11, 67.19]      |
| Subtotal (95% CI)| 209 | 189 | 1.4%  | 2.34 [0.55, 9.92]            |

Total events 6

Heterogeneity: \( \tau^2 = 0.06, df = 2 (P = 0.97); I^2 = 0\%

Test for overall effect: \( Z = 1.16 (P = 0.25) \)
Su QM et al. Telbivudine and entecavir for CHB treatment

1.4.3 12 wk
Zhu et al 4 30 11 30 5.8% 0.36 [0.13, 1.01]
Xu et al 8 30 2 30 1.1% 4.00 [0.92, 17.30]
Zhang et al 6 75 3 65 1.7% 1.73 [0.45, 6.66]
Shi et al 8 40 2 40 1.1% 4.00 [0.90, 17.68]
Zhao et al 3 42 2 39 1.1% 1.39 [0.25, 7.90]
Zheng et al 9 65 2 66 1.0% 4.57 [1.03, 20.34]
Yu et al 21 92 5 85 2.7% 3.88 [1.53, 9.83]
Ye et al 0 46 0 46 Not estimable
Liu et al 0 20 0 20 Not estimable
Subtotal (95% CI) 440 421 14.5% 2.10 [1.36, 3.24]

Total events 59 27
Heterogeneity: $\chi^2 = 15.69$, df = 6 ($P = 0.02$); $I^2 = 62%$
Test for overall effect: $Z = 3.36$ ($P = 0.0008$)

1.4.4 24 wk
Zhu et al 8 30 6 30 3.2% 1.33 [0.53, 3.38]
Xu et al 12 30 6 30 3.2% 2.00 [0.86, 4.63]
Zhao et al 12 75 6 65 3.4% 1.73 [0.69, 4.36]
Shi et al 11 40 7 40 3.7% 1.57 [0.68, 3.64]
Zhao et al 6 42 4 39 2.2% 1.39 [0.42, 4.57]
Zheng et al 16 65 9 66 4.7% 1.81 [0.86, 3.79]
Yu et al 26 92 14 85 7.7% 1.72 [0.96, 3.06]
Ye et al 7 46 2 46 1.1% 3.50 [0.92, 12.60]
Liu et al 0 46 0 46 Not estimable
Subtotal (95% CI) 476 457 32.6% 1.71 [1.29, 2.26]

Total events 107 60
Heterogeneity: $\chi^2 = 2.52$, df = 9 ($P = 0.98$); $I^2 = 0$
Test for overall effect: $Z = 3.71$ ($P = 0.0002$)

1.4.5 48 wk
Zhao et al 10 36 7 36 3.7% 1.43 [0.61, 3.34]
Ding et al 8 30 5 30 2.6% 1.60 [0.59, 4.33]
Zhao et al 15 42 9 39 4.9% 1.55 [0.77, 3.12]
Yu et al 37 92 18 85 9.9% 1.90 [1.18, 3.07]
Ye et al 12 46 4 46 2.1% 3.00 [1.04, 8.62]
Liu et al 4 20 0 20 0.3% 9.00 [0.52, 156.91]
Zhou et al 3 52 3 63 1.4% 1.21 [0.26, 5.75]
Subtotal (95% CI) 318 319 25.0% 1.86 [1.36, 2.54]

Total events 89 46
Heterogeneity: $\chi^2 = 2.97$, df = 6 ($P = 0.81$); $I^2 = 0$
Test for overall effect: $Z = 3.89$ ($P < 0.0001$)

1.4.6 52 wk
Huang et al 25 90 13 90 6.9% 1.92 [1.05, 3.52]
Zhang et al 23 75 11 65 6.2% 1.81 [0.96, 3.43]
Subtotal (95% CI) 165 155 13.1% 1.87 [1.21, 2.90]

Total events 48 24
Heterogeneity: $\chi^2 = 0.02$, df = 1 ($P = 0.89$); $I^2 = 0$
Test for overall effect: $Z = 2.80$ ($P = 0.005$)

1.4.7 60 wk
Zhao et al 15 42 9 39 4.9% 1.55 [0.77, 3.12]
Subtotal (95% CI) 42 39 4.9% 1.55 [0.77, 3.12]

Total events 15
Heterogeneity: Not applicable
Test for overall effect: $Z = 1.22$ ($P = 0.22$)

1.4.8 72 wk
Zhang et al 27 75 15 65 8.5% 1.56 [0.91, 2.67]
Subtotal (95% CI) 75 65 8.5% 1.56 [0.91, 2.67]

Total events 27
Heterogeneity: Not applicable
Test for overall effect: $Z = 1.62$ ($P = 0.10$)

Total (95% CI) 1837 1750 100.0% 1.81 [1.55, 2.13]

Total events 351 183
Heterogeneity: $\chi^2 = 22.15$, df = 30 ($P = 0.85$); $I^2 = 0$
Test for overall effect: $Z = 7.29$ ($P < 0.00001$)
Test for subgroup differences: Not applicable.
Su QM et al. Telbivudine and entecavir for CHB treatment

### Table 2  Sensitivity analysis

| Index | Total HBeAg loss | OR (95% CI) | P value |
|-------|------------------|-------------|---------|
| Excluding the minimum sample size trials | 1.64 [1.31, 2.05] | <0.0010 |
| Using random-effect model | 1.68 [1.35, 2.09] | <0.0001 |
| Using fixed-effect model | 1.69 [1.46, 1.97] | <0.0001 |

OR: Odds ratio; HBeAg: Hepatitis B e antigen.

ability between the two groups. This suggested that both LDT and ETV have rapid and effective anti-viral activity and the result is similar with a large sample size study[29]. In addition, there was also no significant difference in the rate of ALT normalization between the two drugs.

HBeAg is a protein expressed by pre-C gene. HBeAg loss occurs with the rise of immunomodulatory effect which can suppress HBV DNA replication. HBeAg seroconversion has been established as a key marker of treatment response and is associated with improved clinical outcomes. It is one of the significant withdrawal standards for HBeAg-positive patients and suggests that patients can obtain sustained immune response[30]. The results of the meta-analysis showed that at 4 wk and 8 wk of the treatment, the rates of HBeAg loss and HBeAg seroconversion were similar, with no statistical difference between the two groups, while at 12 wk, 24 wk, 48 wk and 52 wk, the rate was higher in the LDT group than in the ETV group, the difference being statistically significant. At 60 wk and 72 wk, there was no significant difference in the rate of HBeAg seroconversion between the two groups. These results suggested that the rates of HBeAg loss and HBeAg seroconversion in the short-term and medium-
term treatment were higher in the LDT group than in the ETV group. So LDT can be used as a primary drug for HBeAg-positive patients. However, its long-term efficacy needs to be further explored.

The higher rate of HBeAg seroconversion during LDT treatment might be associated with the potential immunomodulatory effect of LDT. CHB is a viral as well as an immunological disease. Specific immune function is impaired in the patients with CHB. Many studies suggested that LDT promoted T-helper 1 cytokine and CD4+/CD8+ cell production, but only downregulated programmed death ligand 1, regulatory T cell and T-helper 2 cytokine production. These immunomodulatory effects increase the rate of HBeAg seroconversion.

ETV has a high generative to resistance. The meta-analysis (Figure 2E) showed that the rate of drug-resistance was higher in the LDT group (4.69%) than in the ETV group (0.75%), the difference being statistically significant between the two groups. ETV has a lower drug-resistance than LDT and it is preferred for long-term anti-HBV activity.

The meta-analysis (Figure 2F) showed no severe adverse reactions in the two groups. Although the rate of increased CK in the LDT group was higher than in the ETV group, CK can recover without any intervention, and does not influence the anti-HBV treatment. These results suggest that both LDT and ETV are safe and well tolerated.

COMMENTS

Background

Chronic hepatitis B (CHB) infection is a major health problem affecting over 350 million people worldwide. CHB can lead to a number of life-threatening conditions such as liver failure, liver cirrhosis and hepatocellular carcinoma. Recent studies have shown that telbivudine (LDT) and entecavir (ETV) are the strongest nucleoside analogues in the treatment of CHB. But there are few systematic reviews about the comparison of LDT and ETV.

Research frontiers

LDT is an orally bioavailable L-nucleoside. It can rapidly and effectively suppress HBV DNA replication, but it has a higher drug-resistance. ETV is a new generation nucleoside analogues. It has the advantage of a higher rate of HBV DNA suppression, low drug-resistance and high safety, especially in lamivudine-resistant CHB patients. But the rate of resistance to LDT is lower than that of ETV and HBeAg seroconversion was very low, which is difficult to meet the withdrawal standards.

Innovations and breakthroughs

There are few systematic reviews about the efficacy of LDT and ETV in the CHB treatment. The authors conducted a meta-analysis of the included randomized controlled trials using the Cochrane methodology and explored the efficacy of LDT and ETV for clinical treatment of HBeAg-positive chronic hepatitis B.

Applications

The results of this meta-analysis suggest that LDT and ETV have similar virological and biomedical response, and both are safe and well tolerated. However, LDT has better serological response and higher rate of drug-resistance.

Peer review

This study reviewed 13 trials comparing the effects of telbivudine and entecavir for patients with chronic HBeAg-positive chronic hepatitis B infection. Based on their analyses, the authors conclude that LDT and ETV exert an effective antiviral effect on HBV. Regarding the undetectability and ALT normalization, there was no big difference between the two drugs. The analysis was carefully performed, and the results were clearly presented and summarized, which provided valuable advice for clinical treatment of CHB.

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