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Entecavir versus lamivudine for the treatment of chronic hepatitis B: a systematic review

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The aim of this study was to systematically review the efficacy and safety of entecavir versus lamivudine for the treatment of chronic hepatitis B (CHB). A computerized search of The Cochrane Library (CENTRAL, Issue 5, 2011), MEDLINE (PubMed, 1978-June 2011), EMbase (1974-June 2011) and CNKI (1978-June 2011) databases was conducted. In addition, a manual search was made of the references of the included studies and relevant articles. The searches were restricted to studies published in Chinese or English from the time the database was created to June 2011. Studies were selected according to prespecified inclusion and exclusion criteria and then subjected for quality assessment and data extraction. Meta-analysis was performed using the statistical software (RevMan 5.1.1) provided by the Cochrane Collaboration. A total of 8 studies, all of which were randomized clinical trials (RCTs), involving 2178 patients with CHB were included. Subgroup analyses by treatment duration were conducted. The quality of the evidence was classified as moderate by the GRADED approach for all the included RCTs. Meta-analysis showed the following. Entecavir was associated with significantly improved liver histology, compared with lamivudine (RR 1.16, 95, CI [1.07, 1.26], P = 0.0004). Patients were significantly more likely to experience HBV-DNA loss and have normalized ALT levels when treated with entecavir versus lamivudine for either 48 or 96 weeks (RR 1.65, 95, CI [1.37, 1.98], $P < 0.00001$; RR 1.15, 95, CI [1.11, 1.20], $P < 0.00001$, respectively). There were no statistically significant differences in the proportion of patients who achieved HBeAg loss or HBeAg seroconversion, or who developed adverse events between entecavir and lamivudine treatments (RR 1.03, 95, CI [0.83, 1.26], P = 0.81; RR 0.92, 95, CI [0.75, 1.12], P = 0.39; RR 1.09, 95, CI [0.92, 1.30], P = 0.31, respectively). Current clinical evidence suggests that despite of short- or long-term use, entecavir appears to be more effective than lamivudine in reducing serum HBV-DNA load, improving liver histology, and normalizing ALT in patients with CHB. However, the probability for patients to experience HBeAg loss or HBeAg seroconversion, or the risk for adverse events seems to be similar between entecavir and lamivudine regimens.

1. Introduction

Chronic infection with hepatitis B virus (HBV) is a progressive liver disease. Approximately 350 million people are infected with HBV each year worldwide. Epidemiological investigations show that hepatitis B is a highly prevalent disease in China with a 112-million population of chronic carriers of HBV, accounting for 32% of the disease burden worldwide (Custer et al. 2004; Wu et al. 2005). In the U.S., about 2000 to 4000 deaths per year are related to HBV-associated liver disease (Minino et al. 2007). Thus, there is an urgent need to look for a therapy that is effective for the management of chronic hepatitis B (CHB). The primary goal of treating CHB is to persistently inhibit HBV replication and thereby prevent cirrhosis, liver decompensationand hepatocellular carcinoma (Liaw et al. 2003; Wilt et al. 2008; Feld et al. 2009). Lamivudine (LVD, trade name Heptodin and others) may significantly inhibit HBV replication by specifically block the synthesis of hepadnavirus DNA (Yao et al. 1999). However, long-term use of LVD is usually associated with an increased risk of developing resistance to the treatment. A report shows that the proportion of patients with CHB who developed clinical resistance to LVD was about 24% after 1 year of treatment and 70% or more after 4 years (Lai et al. 2003). Entecavir (ETV), marketed as Baraclude and others, is an anti-HBV agent approved for marketing in China in November 2005. ETV is a guanine nucleotide analogue with potent and selective inhibitory activity against HBV DNA replication. Compared with other nucleoside drugs, ETV is associated with a very lower risk for resistance in treatment-naïve patients (Lau 2008; Jiang et al. 2009). Numerous *in vitro* experiments, animal models and human clinical trials have showed that ETV has a strong inhibitory effect on viruses and a low risk for resistance. However, most of the randomized controlled trials (RCTs) are small-scale clinical trials with less convincing conclusions due to insufficient data and a small sample size. In the present study, we used the Cochrane systematic review methodology to collect, evaluate and analyze published RCTs to provide evidence-based support for clinical use of ETV for the treatment of CHB.

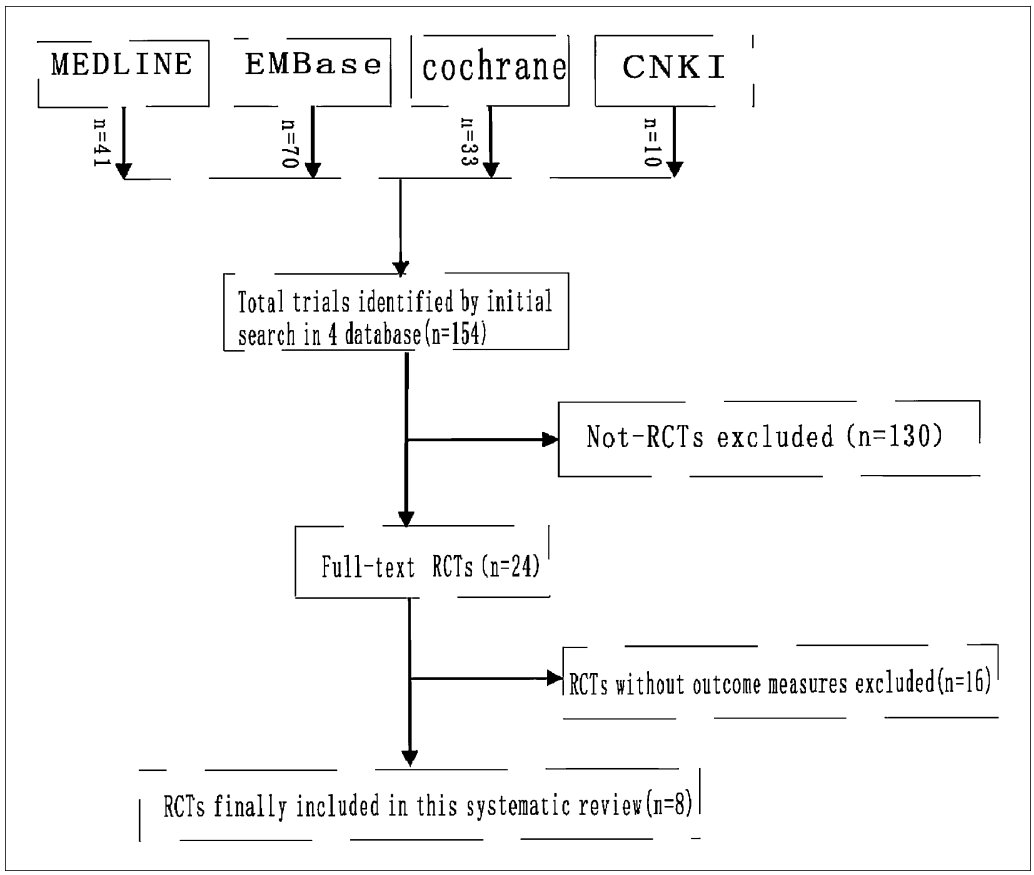

Fig. 1: Flow of study inclusion and exclusion

2. Investigations

2.1. Inclusion and exclusion criteria

2.1.1. Diagnostic criteria

According to the National Institute of Health Workshop on Management of Chronic Hepatitis B in 2000, CHB is defined as chronic necroinflammation of the liver caused by persistent HBV infection and patients with CHB may be HBeAg positive or HBeAg negative (Lok and McMahon 2001; Lok and McMahon 2004).

A diagnosis of CHB may be considered if (1) HBeAg remains positive for more than 6 months; (2) serum HBV-DNA > 10^5 copies/mL; (3) alanine transaminase (ALT) persistently or intermittently elevated; and (4) chronic liver inflammation on biopsy (necroinflammatory score > 4).

2.1.2. Type of study

Randomized controlled trials (RCTs) comparing ETV with LVD in patients with CHB were included if they were published in Chinese or English in full text, regardless of use of allocation concealment or blinding.

2.1.3. Subjects

Subjects eligible for study entry were nucleoside-naïve patients with HBeAg-positive or HBeAg-negative CHB, despite of race, age and sex. Patients were excluded if they were HBV carriers coinfected or superinfected with other hepatitis viruses, if they had decompensated liver disease or hepatocellular carcinoma, or if they had received antivirals and immunomodulators for CHB within one year prior to the initiation of nucleoside treatment.

2.1.4. Interventions

ETV was evaluated as an experimental treatment while LVD was used as a control treatment.

2.1.5. Outcome measures

Primary outcome measures included improvement of liver histology and loss of serum HBV DNA (as determined by polymerase chain reaction [PCR] assay). Secondary endpoints included normalization of serum ALT, loss of serum HBeAg, HBeAg seroconversion, HBsAg loss and incidence of adverse events (including headache, common cold, upper respiratory tract infection, gastrointestinal disorders, fatigue, and increased ALT or AST during treatment and follow-up).

2.2. Search strategy

Three English-language electronic databases including The Cochrane Library (CENTRAL, Issue 5, 2011), MEDLINE (PubMed, 1978-June 2011) and EMbase (1974-June 2011) were searched, using English words “chronic hepatitis B”, “entecavir”, “lamivudine”, “randomized controlled trial” as search terms. For the search of CNKI (1978-June 2011), a Chinese-language electronic database, Chinese equivalents of the aforementioned English words were used as search terms.

2.3. Data extraction and quality assessment

Data extraction was conducted independently by two reviewers using a uniform extraction form. The extracted data were cross-checked. The authors of the study identified would be contacted to provide a better understanding of the conduct of the study if necessary. Discrepancies were resolved by discussion or referral

Table 1: Characteristics of the included studies

Studies included	No. of patients		Interventions (n)		Duration of follow-up (weeks)	Duration of treatment (weeks)	No. of patients lost to follow-up (n)	ITT analysis performed
	Experimental treatment	Control treatment	Experimental treatment	Control treatment				
Chang et al. (2006)	354	355	ETV 0.5 mg qd	LVD 100 mg qd	24	48	12	yes
Gish et al. (2007)	243	164	ETV 0.5 mg qd	LVD 100 mg qd	24	96	4	yes
Lai et al. (2002)	46	41	ETV 0.5 mg qd	LVD 100 mg qd	12	24	not reported	no
Lai et al. (2006)	325	313	ET V 0.5 mg qd	LVD 100 mg qd	24	48	not reported	yes
Ren et al. (2007)	21	21	ETV 0.5 mg qd	LVD 100 mg qd	24	48	0	yes
Yao et al. (2007)	258	261	ET V0.5 mg qd	LVD 100 mg qd	24	48	4	yes
Yao et al. (2008)	193	145	ETV 0.5 mg qd	LVD 100 mg qd	24	96	5	yes
Chen and Qiu (2009)	118	69	ETV 0.5 mg qd	LVD 100 mg qd	not mentioned	48	not reported	no

ETV = entecavir, LVD = lamivudine

to a third reviewer. Methodological quality of the included RCTs was assessed using the criteria (randomization, allocation concealment, blinding, complete outcome data, selective outcome reporting, and other potential biases) described by Higgins et al. (2003) in the Cochrane Reviewers' Handbook 5.1. If any of the included trials had a follow-up loss of greater than 20%, an attempt was made to determine possible causes of loss to follow-up and intention-to-treat (ITT) analysis was conducted. After meta-analysis of the included studies was done, the evidence of the included trials was graded using the GRADEpro software (version 3.2.2).

2.4. Statistical analysis

Statistical analysis was performed using the RevMan software (version 5.1.1) from The Cochrane Collaboration. Results were expressed as weighted mean difference (WMD) and its 95% confidence interval (CI) for continuous variables and as relative risk (RR) and its 95% CI for categorical variables. Each effect size was expressed as 95% CI. For hypothesis test, the U test was used and results were expressed as Z and p values. The between-group differences were considered as having statistical significance if $P \leq 0.05$. Heterogeneity among the results of the included trials was evaluated by the chi square (χ^2) test. The extent of heterogeneity among studies was determined using I^2 where a higher I^2 value indicates a greater heterogeneity. When the heterogeneity test yielded a P value ≤ 0.10, an attempt was made to see if the heterogeneity was due to differences in treatment duration, dosage, disease severity, or control selection. If the heterogeneity was due to these differences, then subgroup analysis, Breslow-Day test and regression approximation were applicable. Pooled analysis was performed using a fixed effects model when there was no statistical heterogeneity or using a random effects model if there was statistical heterogeneity. Descriptive analysis was done when it was not able to conduct meta-analysis due to the presence of significant clinical or methodological heterogeneity or due to incomplete data available. If there was significant statistical heterogeneity due to differences in methodological quality across the included studies, sensitivity analysis was performed after excluding the low-quality studies.

3. Results

3.1. Results of literature search and characteristics of the included trials

An initial search identified 154 articles, including 41 from PubMed, 33 from The Cochrane Library, 70 from EMbase, and 10 from CNKI. After reading the title, abstract and full text of the identified articles, 8 RCTs were finally included (Lai et al. 2002; Chang et al. 2006; Lai et al. 2006; Gish et al. 2007; Ren et al. 2007; Yao et al. 2007; Yao et al. 2008; Chen and Qiu 2009). Of the 8 RCTs, 7 were published in English language, and 1 in Chinese language. The 8 RCTs involved a total of 2178 patients with CHB, with 1119 receiving ETV and 1059 treated with LVD. Figure 1 summarizes the flow of study inclusion and exclusion. Chang et al. 2006 (Chang et al. 2006) and Gish et al. 2007 (Gish et al. 2007) reported the same RCT, as did Yao et al. 2007 (Yao et al. 2007) and Yao et al. 2008 (Yao et al. 2008). Treatment duration was either 48 or 96 weeks. The characteristics of each included study are shown in Table 1.
Assessment of methodological quality of the included RCTs was conducted using the Risk of Bias tool described in the Cochrane Reviewers' Handbook 5.1.1 (Table 2).

3.2. Results of meta-analysis

3.2.1. Improvement of liver histology

Improvement of liver histology was reported in two studies (Chang et al. 2006; Lai et al. 2006). Both studies were double-

Table 2: Assessment of methodological quality of the included studies

Studies included	Randomization	Allocation concealment	Blinding	Complete outcome data	Selective outcome reporting	Other potential sources of bias
Chang et al. (2006)	unclear	low risk	low risk	low risk	low risk	unclear
Gish et al. (2007)	low risk	low risk	low risk	low risk	low risk	unclear
Lai et al. (2002)	low risk	low risk	low risk	low risk	low risk	unclear
Lai et al. (2006)	unclear	low risk	low risk	low risk	low risk	unclear
Ren et al. (2007)	unclear	unclear	unclear	low risk	low risk	unclear
Yao et al. (2007)	unclear	unclear	unclear	low risk	low risk	unclear
Yao et al. (2008)	unclear	unclear	unclear	low risk	low risk	unclear
Chen and Qiu (2009)	unclear	unclear	unclear	low risk	low risk	unclear

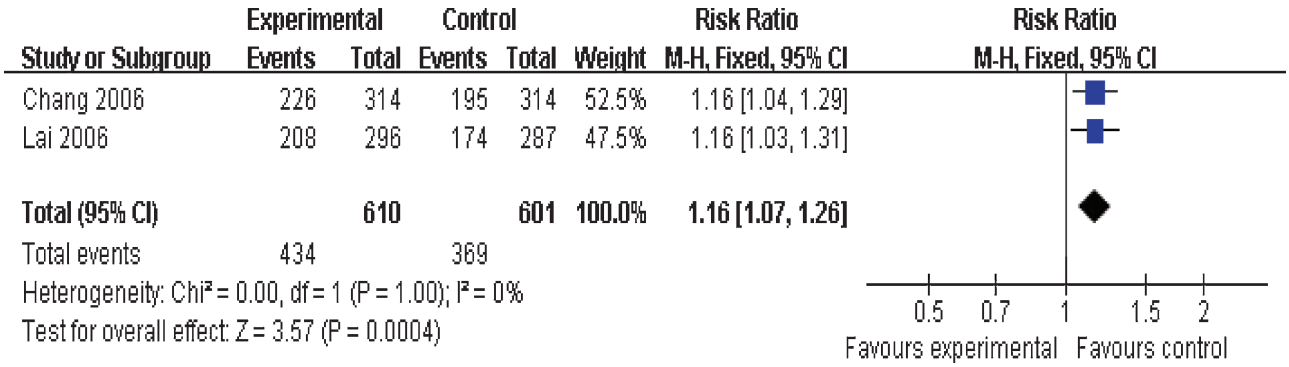

Fig. 2: Meta-analysis comparing ETV with LVD in improving liver histology

blind phase III clinical trials with a treatment duration of 48 weeks. There was no statistical heterogeneity between studies (P = 1.00, I^2 = 0%). Meta-analysis showed that patients with CHB were significantly more likely to have improved liver histology with ETV than with LVD (RR = 1.16, 95% CI [1.07, 1.26], P = 0.0004) (Fig. 2).

3.2.2. *Loss of serum HBV-DNA (PCR)*

HBV-DNA loss was reported in all the 8 studies (Lai et al. 2002; Chang et al. 2006; Lai et al. 2006; Gish et al. 2007; Ren et al. 2007; Yao et al. 2007; Yao et al. 2008; Chen and Qiu 2009). Studies were classified by treatment duration and then subjected to subgroup analysis. In a subgroup analysis including 6 studies with a treatment duration of 48 weeks, statistical heterogeneity was found across studies ($P < 0.00001$, $I^2 = 86\%$). Meta-analysis using a random effects model showed that ETV was significantly more effective than LVD in helping patients to achieve loss of HBV-DNA (RR 1.56, 95%CI [1.27, 1.91], $P < 0.0001$). There was no statistical heterogeneity between the remaining two studies reporting achievement of HBV-DNA loss by 96-week treatment (P = 0.40, I^2 = 0%). Meta-analysis showed that HBV-DNA loss occurred significantly more often with ETV than with LVD (RR 1.90, 95%CI [1.63, 2.20], $P < 0.00001$). Patients with CHB had a higher chance to achieve undetectable HBV-DNA (PCR) when treated with ETV versus LVD for either 48 or 96 weeks (Fig. 3).

3.2.3. *Normalization of serum ALT*

Normalization of serum ALT was reported in the 8 studies (Lai et al. 2002; Chang et al. 2006; Lai et al. 2006; Gish et al. 2007; Ren et al. 2007; Yao et al. 2007; Yao et al. 2008; Chen and Qiu 2009). Again, subgroup analysis by treatment duration was conducted. There was no statistical heterogeneity across 6 studies with a treatment duration of 48 weeks (P = 0.40, I^2 = 2%). Meta-analysis showed that ETV was associated with a significantly higher proportion of patients who had normalized ALT levels, compared with LVD (RR = 1.15, 95%CI [1.09, 1.21], $P < 0.00001$). No statistical heterogeneity was found between the remaining two 96-week-treatment studies (P = 0.95, I^2 = 0%). Meta-analysis revealed that ETV was significantly more efficacious in normalizing ALT levels compared with LVD (RR 1.17, 95%CI [1.08, 1.25], $P < 0.0001$). Compared with LVD, ETV was associated with better ALT nor-

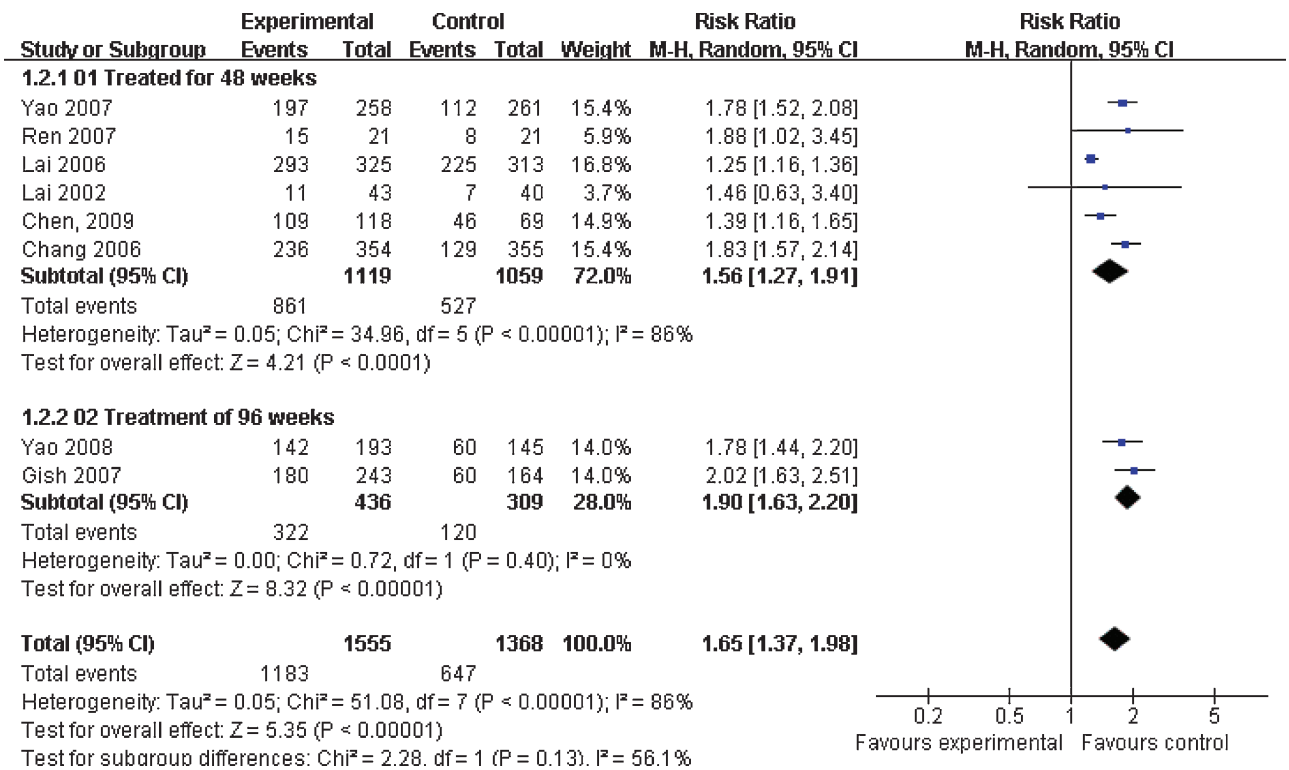

Fig. 3: Meta-analysis comparing ETV with LVD in achieving HBV-DNA loss (PCR)

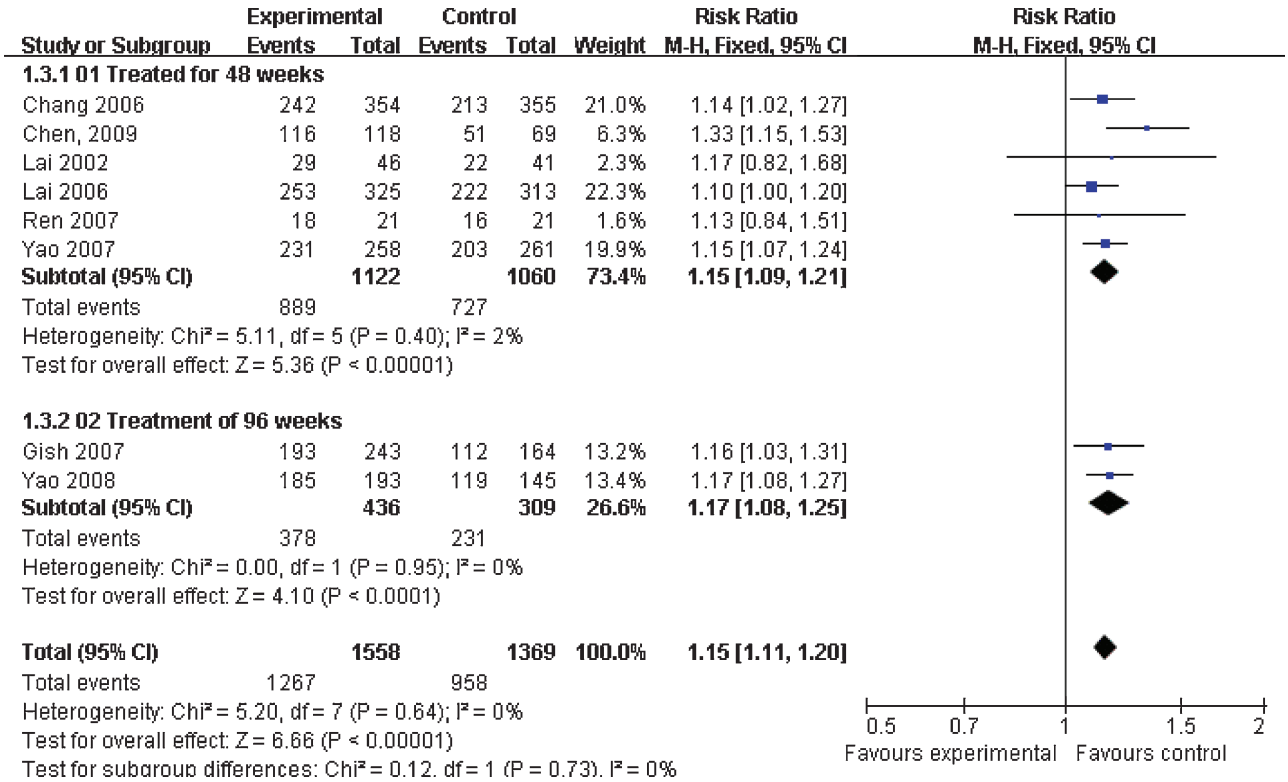

Fig. 4: Meta-analysis comparing ETV with LVD in normalizing serum ALT

malization in patients with CHB, regardless of the duration of treatment (48 or 96 weeks) (Fig. 4).

3.2.4. *Loss of serum HBeAg*

HBeAg loss was reported in 4 studies (Lai et al. 2002; Chang et al. 2006; Ren et al. 2007; Chen and Qiu 2009). Patients in the 4 studies all received 48 weeks of treatment. There was no statistical heterogeneity among studies ($P = 0.44$, $I^2 = 0\%$). Meta-analysis found that there were no statistically significant differences in achievement of HBeAg loss between ETV-treated and LVD-treated patients with CHB (RR 1.03, 95%CI [0.83, 1.26], $P = 0.81$) (Fig. 5).

3.2.5. *HBeAg seroconversion*

HBeAg seroconversion was reported in 6 studies (Lai et al. 2002; Chang et al. 2006; Gish et al. 2007; Ren et al. 2007; Yao et al. 2007; Yao et al. 2008). No statistical heterogeneity was observed across studies ($P = 0.32$, $I^2 = 14\%$). Meta-analysis showed that achievement of HBeAg seroconversion was similar in CHB patients treated with ETV or LVD (RR 0.92, 95% CI [0.75, 1.12], $P = 0.39$) (Fig. 6).

3.2.6. *Incidence of drug-related adverse events*

Incidence of drug-related adverse events was reported in 6 studies (Lai et al. 2002; Chang et al. 2006; Lai et al. 2006; Gish et al. 2007; Yao et al. 2007; Yao et al. 2008). There was no statistical heterogeneity among studies ($P = 0.49$, $I^2 = 0\%$). Meta-analysis demonstrated that both ETV and LVD were associated with a similar incidence of adverse events in patients with CHB (RR 1.09, 95% CI [0.92, 1.30], $P = 0.31$) (Fig. 7).

3.2.7. *Assessment of the quality of the included Studies' evidence by GRADE*

Figure 8 shows the quality of the included RCTs' evidence assessed by an approach developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group (Guyatt et al. 2011). The GRADE system classifies the quality of evidence into the following four grades:

- High quality: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

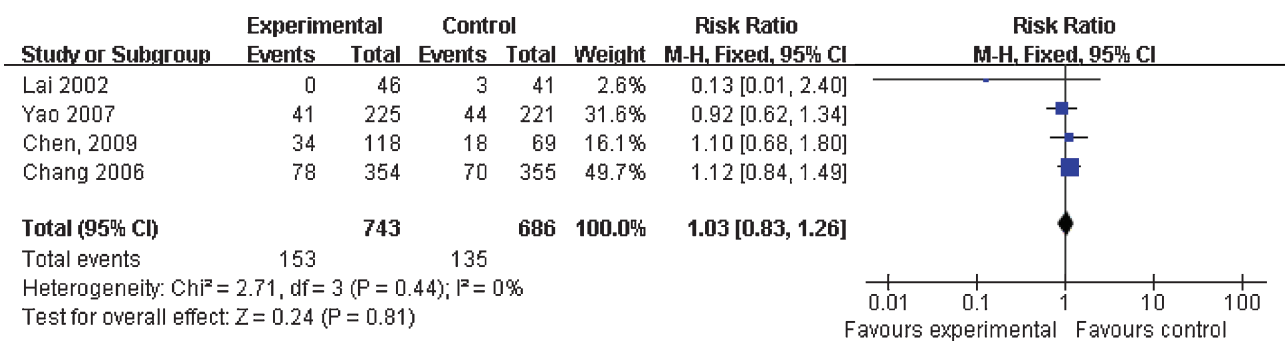

Fig. 5: Meta-analysis comparing ETV with LVD in achieving HBeAg loss

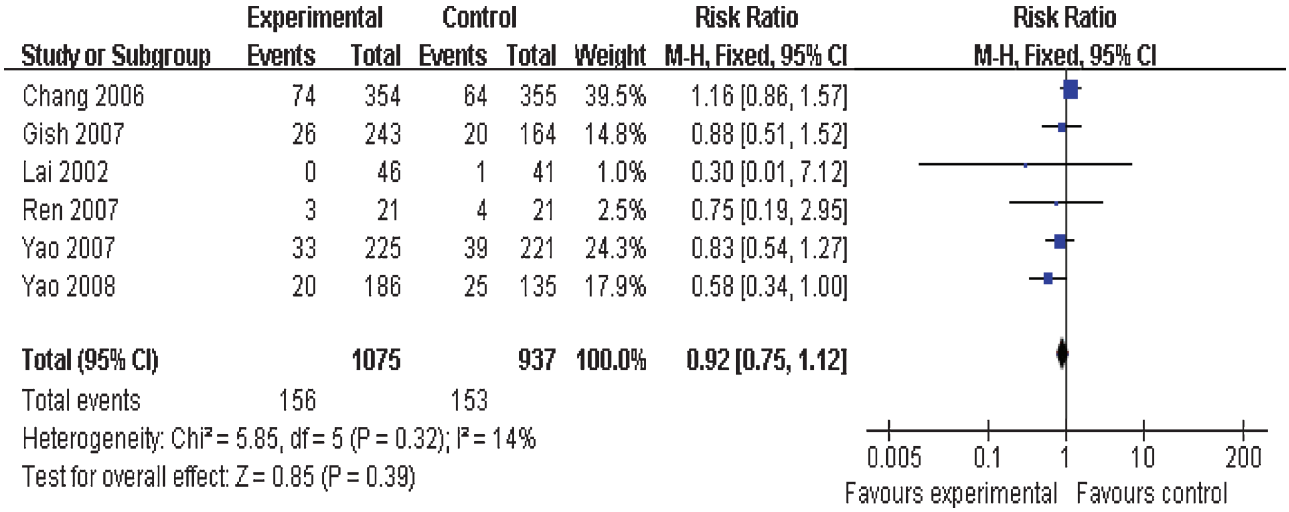

Fig. 6: Meta-analysis comparing ETV with LVD in achieving HBeAg seroconversion

- Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: We are very uncertain about the estimate.

The quality of the evidence was graded as moderate for all the studies included in this review.

4. Discussion

In this study, we conducted a search of clinical trials which evaluated the efficacy and safety of ETV and LVD for the treatment of CHB and were published in Chinese- or English-language journals as of June 2011. Meta-analysis showed that ETV had a higher efficacy in inhibiting HBV-DNA replication, reducing transaminase levels and improving liver histology and was not associated with an increased risk for adverse events, compared with LVD. RCTs included in this systematic review all had a moderate quality of evidence. The strength of the results of these studies may have been weakened due to a possible risk of bias caused by some limitations in study design and implementation. In the future, randomized controlled clinical trials that have a higher quality are warranted.

4.1. Methodological quality of the included studies

This systematic review included 8 RCTs with comparable baseline characteristics (age, sex). Although all the 8 studies were claimed to be RCTs, only 2 RCTs provided a clear description of the randomization methods used, while the remaining 6 offered no such description. Four RCTs described and used adequate allocation concealment whereas the other 4 did not mention or provide a clear description of allocation concealment and therefore were considered as having a moderate risk of selection bias. Four RCTs used blinding while the remaining 4 either did not use blinding or did not explicitly report the blinding procedure and were considered as having a moderate risk of measurement bias. Five RCTs reported losses to follow-up, dropouts and exclusions, and 6 RCTs performed ITT analysis and therefore had a low risk of follow-up bias. None of the 8 RCTs selectively reported outcomes, so the risk of reporting bias was low. Although some limitations regarding study design and implementation (methodological quality) existed in the studies included in this systematic review, consistency and precision of results was good and there was no indirect evidence or publication bias. Therefore, the quality of the evidence was classified by the GRADE system as moderate and the risk of bias was judged as moderate (Fig. 8).

4.2. Limitations

Some methodological limitations that may have affected the internal validity of the included studies' results were inadequate randomization, unclear allocation concealment, poor implementation of blinding procedure, and a short duration of follow-up. In addition, there were differences among the included RCTs, with respect to treatment duration, disease severity, and time points of

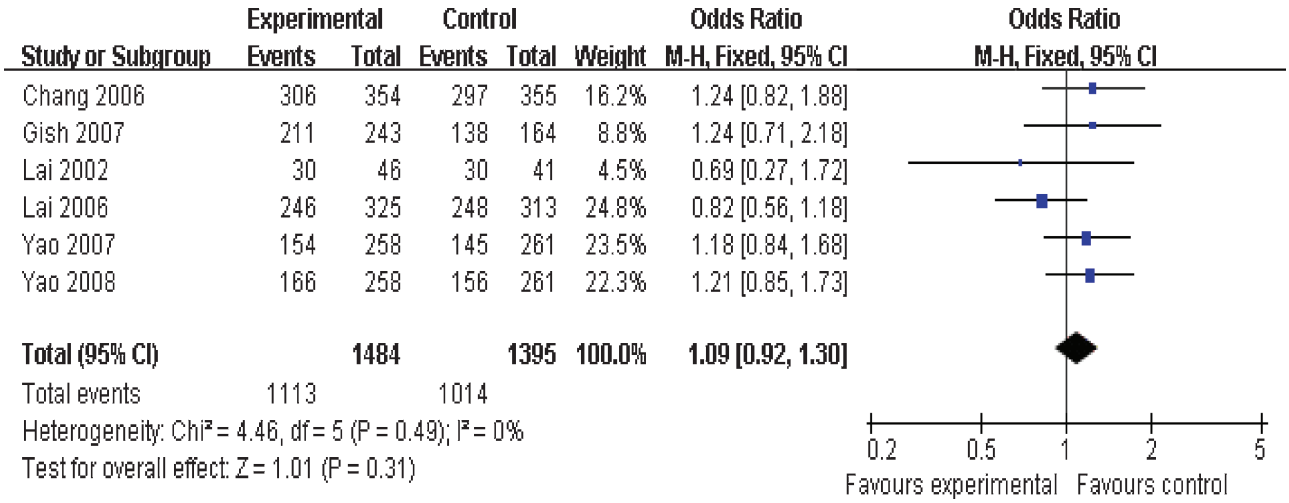

Fig. 7: Meta-analysis comparing incidence of adverse events associated with ETV or LVD

enticavir for Chronic Hepatitis B

Patient or population: patients with Chronic Hepatitis B
Settings: nanning
Intervention: enticavir

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk enticavir	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Histologic Improvement at Week 48 (Primary Study End Point).	Study population		RR 1.16 (1.07 to 1.26)	1211 (2 studies)	⊖⊖⊖⊖ moderate	
	614 per 1000	712 per 1000 (657 to 774)				
	Medium risk population					
	614 per 1000	712 per 1000 (657 to 774)				
HBV DNA <300 copies/ml - Treated for 48 weeks	Study population		RR 1.56 (1.27 to 1.91)	2178 (6 studies)	⊖⊖⊖⊖ moderate	
	498 per 1000	777 per 1000 (632 to 951)				
	Medium risk population					
	405 per 1000	632 per 1000 (514 to 774)				
HBV DNA <300 copies/ml - Treatment of 96 weeks	Study population		RR 1.9 (1.63 to 2.2)	745 (2 studies)	⊖⊖⊖⊖ moderate	
	388 per 1000	737 per 1000 (632 to 854)				
	Medium risk population					
	390 per 1000	741 per 1000 (636 to 858)				
ALT normalization - Treated for 48 weeks	Study population		RR 1.15 (1.09 to 1.21)	2182 (6 studies)	⊖⊖⊖⊖ moderate	
	686 per 1000	789 per 1000 (748 to 830)				
	Medium risk population					
	724 per 1000	833 per 1000 (789 to 876)				
ALT normalization - Treatment of 96 weeks	Study population		RR 1.17 (1.08 to 1.25)	745 (2 studies)	⊖⊖⊖⊖ moderate	
	748 per 1000	875 per 1000 (808 to 935)				
	Medium risk population					
	752 per 1000	880 per 1000 (812 to 940)				
Loss of HBeAg	Study population		RR 1.03 (0.83 to 1.26)	1429 (4 studies)	⊖⊖⊖⊖ moderate	
	197 per 1000	203 per 1000 (164 to 248)				
	Medium risk population					
	198 per 1000	204 per 1000 (164 to 249)				
HBeAg seroconversion	Study population		RR 0.92 (0.75 to 1.12)	2012 (6 studies)	⊖⊖⊖⊖ moderate	
	163 per 1000	150 per 1000 (122 to 183)				
	Medium risk population					
	178 per 1000	164 per 1000 (133 to 199)				
adverse event	Study population		OR 1.09 (0.92 to 1.3)	2879 (6 studies)	⊖⊖⊖⊖ moderate	
	727 per 1000	744 per 1000 (710 to 776)				
	Medium risk population					
	762 per 1000	777 per 1000 (747 to 806)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Fig. 8: The quality of the included RCTs' evidence rated by GRADE

and tools used for outcome assessment. Therefore, the validity of the pooled statistics may have been affected due to presence of varying degrees of bias and confounding factors although subgroup analysis by treatment duration was performed to eliminate the effect of heterogeneity on the results. Finally, there may be a risk of bias in language distribution of the included articles because our search was restricted to RCTs published in English or Chinese languages and only 1 Chinese-language article was included along with 7 English-language reports.

4.3. Analysis of efficacy and safety

Our systematic review of 8 RCTs showed the following results. ETV had a significant advantage over LVD with respect to hepatohistological improvement, HBV-DNA loss, and ALT normalization, especially when it was used for a prolonged period of time. This finding is consistent with the conclusions drawn by Shi et al. (2010) and Liu et al. (2009). ETV was not more effective than LVD in helping patients with CHB to achieve HBeAg loss or HBeAg seroconversion, which is also in line with the conclusions by Shi et al. (2010). Regarding safety and adverse events, ETV was as safe as LVD and had few side effects. Both ETV and LVD appear to be safe options for long-term treatment of CHB. With respect to resistance, LVD has no longer been recommended as a first line treatment for CHB in guidelines in countries like the U.S. since 2007 because chronic users of LVD have been found to be at a high risk of developing resistance to the treatment.

4.4. Significance for clinical practice and implications for the future

In this paper, we systematically reviewed the effects of ETV versus LVD, when given at the same dose for different durations, on various primary endpoints at different time points in patients with CHB. Our results showed that ETV was as safe as and more effective than LVD in improving virological, biochemical, and histological outcomes. However, ETV was not associated with a significant increase in HBeAg or HBeAb seroconversion. Studies have suggested that, compared with LVD, ETV appears to be a more reasonable option for the clinical treatment of CHB patients who have histopathologically-confirmed active inflammation or fibrosis, active viral replication, and persistently elevated ALT levels. In addition, ETV has a good safety profile even when used for a prolonged period of time. The 8 RCTs included in our review provided no direct evidence supporting a potential of ETV or LVD to reduce mortality, or liver cancer or cirrhosis occurrence in patients with CHB. Moreover, in the included RCTs, outcomes such as mortality and incidences of cirrhosis and liver cancer were less frequently assessed. Most of the included studies were designed to investigate short-term treatment efficacy by evaluating biological, virological and histological parameters. Therefore, the effects of ETV on long-term mortality and hepatocellular carcinoma occurrence in patients with CHB need to be further investigated in large, multicenter, randomized, controlled trials. To minimize inter-study heterogeneity and improve methodological quality, future clinical should focus on standardization of dosage and duration of treatment, and should conduct long-term follow-up of adverse events, provide detailed information on losses to follow-up and exclusions, and the use of ITT analysis. In conclusion, researchers are encouraged to follow the ICMJE clinical trial registration policy (De Angelis et al. 2005) and the CONSORT (Consolidated Standards of Reporting Trials) statement (Moher et al. 2001) to conduct well-designed RCTs of higher methodological quality so as to provide stronger evidence with minimal selection and measurement bias for the clinical treatment of CHB.

Declaration of interest: The authors report no declarations of interest. The authors alone are responsible for the content and writing of this article.

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