International Scholars Journals

International Journal of Virology and Parasitology, Vol. 12 (1), pp. 001-006, January, 2023. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Comparison of the efficacy of entecavir and lamivudine in the treatment of chronic hepatitis B: A meta-analysis

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Accepted 17 November, 2022

Some researches demonstrate that entecavir increases the incidence of virological and biochemical responses compared to lamivudine, although, they have shown inconsistent response rates. A meta-analysis was conducted to compare the efficacy of entecavir and lamivudine for chronic hepatitis B treatment. Two independent researchers identified pertinent clinical controlled trials. Our analysis includes nine case-control studies, which had 1251 entecavir groups and 1188 lamivudine groups. Analyses were performed with STATA version 9.0. Rates of virology and biochemical responses and HBeAg clearance and seroconversion were used as primary efficacy measures. Greater virological and biochemical responses rates were observed with entecavir to lamivudine after treatment of 48 weeks (odds ratio (OR) = 3.422, 95% confidence intervals (CI) = 2.349 - 4.985, P = 0.000; OR = 2.173, 95% CI = 1.462 - 3.230, P = 0.000, respectively), but no statistically significant differences were observed between cases and controls for clearance and seroconversion of HBeAg (P > 0.05). Safety and adverse-event profiles were similar in the two groups. In conclusion, this meta-analysis suggested that entecavir increases the incidence of virological and biochemical responses compared with lamivudine after treatment for 48 weeks.

Key words: Chronic hepatitis B, entecavir, lamivudine, treatment, meta-analysis.

INTRODUCTION

Hepatitis B virus (HBV) infection is a serious global public health problem. It is estimated that 400 million people worldwide are chronically infected with HBV and most of them live in Asia or the west Pacific regions, especially in China (Schiff, 2006). Chronically, infected patients with persistently high serum HBV DNA levels are at higher risk of progressive liver disease, cirrhosis, hepatic; decompensation, HCC and death (Iloeje et al., 2006 Chen et al., 2006). Therefore, treatment of chronic hepatitis B (CHB) aimed at sustained inhibition of HBV replication (Lok and McMahon, 2007).

Currently, interferon alpha and four nucleoside analogues have been approved for the treatment of CHB. Lamivudine is the first potentially non-cytotoxic oral nucleoside analogue approved for the treatment of chronic hepatitis B. Studies of long-term lamivudine treatment in patients with HBeAg-positive CHB have found that maintenance of virologic suppression is associated with improved histologic findings in the liver (Lai et al., 1998; Dienstag et al., 1999). Entecavir is a potent and selective inhibitor of HBV DNA polymerase. *In vitro* studies of entecavir has a low EC_{50} (4 nM) for wild-type virus and that entecavir is > 300-fold more potent

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Abbreviations: ALT, Alanine aminotransferase; **HBeAg,** hepatitis B antigen; **EC_{50},** median effect concentration; **HCC,** hepatocellular carcinoma.

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against wild-type virus than other antiviral agents that are either approved or under development (for example, lamivudine, adefovir, telbivudine or tenofovir) (Innaimo et al., 1997). Recently, some randomized controlled clinical trials have compared the efficacy of entecavir and lamivudine in the treatment of chronic hepatitis B. These researches demonstrate that entecavir increases the incidence of virological and biochemical responses, although, some studies have shown inconsistent response rates. Meta-analysis is a powerful method for quantitatively summarizing the results from different studies (Sacks et al., 1996). One of the advantages is to increase sample size, which may reduce the probability that random error will produce false-positive or false-negative association. Thus, we conducted this meta-analysis of these trials to assess the evidence obtained on the efficacy of entecavir treatment and its comparison with that of lamivudine in chronic HBV infection.

MATERIALS AND METHODS

Literature search strategy

All articles were retrieved by searching PUBMED, EMBASE, CNKI (China National Knowledge Infrastructure), CBM (China Biology Medical) and WanFang literature database. The key words used were as follows: ''chronic hepatitis B'' or ''CHB'', ''entecavir'', ''lamivudine'' and ''treatment''. The last search was updated on September 9, 2010. The search was done without restriction on language and it focused on studies that had been conducted on human subjects. The reference lists of reviews and retrieved literature were searched simultaneously. Abstracts and unpublished reports were not considered.

Inclusion and exclusion criteria

To be included in the meta-analysis, all articles must meet these criteria: (1) the study was designed as randomized controlled trials (RCTs) or non-randomized controlled trials (NRCTs); (2) full text was available for the published study; (3) eligible patients were at least 16 years of age, according with CHB diagnostic and antiviral treatment criteria (Lok and McMahon,2009), HBeAg-positive or negative, naive antiviral treatment; (4) the study provided the number of patients of entecavir cases and lamivudine controls; (5) the study provided the number of patients of loss of HBV DNA, ALT normalization, HBeAg clearance and seroconversion in cases and controls. Major reasons for exclusion from our studies were: (1) co-infection with hepatitis C virus, hepatitis D virus or human immunodeficiency virus; other forms of liver disease; (2) duplicates; (3) no usable data reported.

Data extraction

In order to retrieve articles as completely and correctly as possible, two investigators in our group extracted data independently using a standardized form and reached consensus on all items. For each study, the following information was obtained: name of the first author, year of publication, country, origin of the studied population, number of subjects in each case or control groups, number of patients of loss of HBV DNA, ALT normalization, HBeAg clearance and seroconversion and the results of the study. Controversial literatures were selected for this study after discussion.

Definition of main outcomes

Virological responses were defined as undetectable of HBV DNA in the serum by polymerase chain reaction (PCR) assay. Biochemical responses were defined as ALT normalization. HBeAg clearance was defined as disappearance of HBeAg in the serum in HBeAg positive CHB. HBeAg seroconversion was defined as disappearance of HBeAg and HBeAb occurred in HBeAg positive CHB.

Statistical analysis

The statistical analysis was conducted by using Stata 9.0 (StataCorp, College Station, TX USA) and $P \leq 0.05$ was considered to be statistically significant. In this study, we used the odds ratio (OR) of the main outcomes as the measure of efficacy. The 95% confidence interval (CI) for the combined OR is also provided. Statistical heterogeneity was measured by using the Q-statistic ($P \leq 0.10$ was considered to be representative of statistically significant heterogeneity). The effect of heterogeneity was also quantified using the I^2-statistic which measures the degree of inconsistency in the studies by calculating what percentage of the total variation across studies is due to heterogeneity rather than by chance. A fixed effects model was used when there was no heterogeneity of the results of the trials. Otherwise, the random effects model was used. For sensitivity analysis of dichotomous outcomes, we used two methods independently. Firstly, we deleted small weight studies included in the meta-analysis each time. Secondly, trim and fill method was used. Several statistical methods were used to assess the potential for publication bias described follows. Visual inspection of asymmetry in funnel plots was conducted. Begg's rank correlation method and the Egger weighted regression method were also used to statistically assess the publication bias ($P \leq 0.05$ was considered to be representative of statistically significant publication bias).

RESULTS

Study characteristics

A total of 31 literatures were searched. After careful reading, 9 literatures were chosen to perform the meta-analysis which contained 1251 cases and 1188 controls (Chang et al., 2006; Lai et al., 2006; Yao et al., 2007; Ren et al., 2007; Cai et al., 2007; Chen et al., 2008, 2009; An et al., 2009; Wang and Li, 2009). All of the cases were entecavir monotherapy groups and all of the controls were lamivudine monotherapy groups. Characteristics of studies included in the meta-analysis are presented in Table 1.

Virological responses

Greater virological response rates were observed for patients given entecavir monotherapy when compared with lamivudine monotherapy groups (76.6 versus 53.6%, OR = 3.422, 95% CI = 2.349 - 4.985, P = 0.000) (Figure 1

Table 1. Characteristics of studies included in the meta-analysis.

Study	Study Design	Virological response		Biochemical response		HBeAg clearance		HBeAg seroconversion	
		ETV	LMV	ETV	LMV	ETV	LMV	ETV	LMV
Chang (2006)	RCT, DB	236/354	129/355	242/354	213/355	78/354	70/355	74/354	64/355
Lai (2006)	RCT, DB	293/325	225/313	253/325	222/313	-	-	-	-
Yao (2007)	RCT, DB	147/258	112/261	231/258	203/261	41/225	44/221	33/225	39/221
Ren (2007)	RCT	15/21	8/21	18/21	16/21	-	-	4/21	3/21
Cai (2007)	RCT, DB	14/16	5/17	14/16	13/17	0/12	1/15	0/12	1/15
Chen (2008)	NRCT	32/37	34/40	19/37	19/40	8/37	7/40	-	-
Chen (2009)	RCT	109/118	46/69	116/118	51/69	34/118	18/69	28/118	13/69
An (2009)	NRCT	39/42	30/42	38/42	31/42	13/33	6/34	10/33	4/14
Wang (2009)	RCT	73/80	48/70	75/80	53/70	-	-	12/48	3/40

RCT, randomized controlled trials; NRCT non-randomized controlled trials; DB, double blind; ETV, entecavir; LMV, lamivudine.

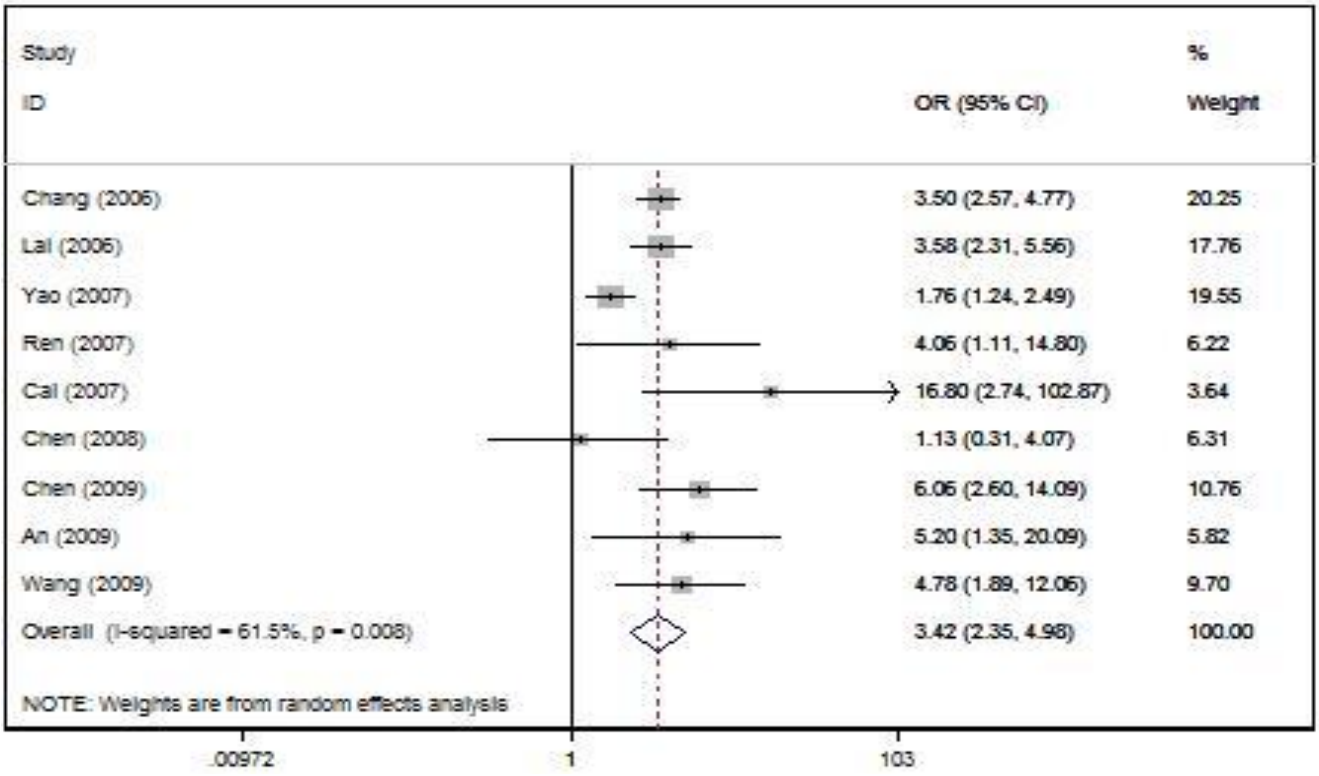

Figure 1. Meta-analysis of the nine trials comparing virological responses in ETV and LMV treated patients with chronic hepatitis B after treatment of 48 weeks.

and Table 2).

Biochemical responses

Greater biochemical responses rates were observed for patients given entecavir monotherapy when compared with lamivudine monotherapy groups (80.4 versus 68.3%, OR = 2.173, 95% CI = 1.462 - 3.230, P = 0.000) (Figure 2 and Table 2).

HBeAg clearance and seroconversion

No statistically significant differences were observed between cases and controls for clearance and sero-conversion of HBeAg (22.3 versus 19.9%, OR = 1.127, 95% CI = 0.879 - 1.445, P = 0.345; 19.9 versus 17.3%, OR = 1.207, 95% CI = 0.933 - 1.562, P = 0.153, respectively) (Table 2).

Table 2. Summary of meta-analysis of comparing the efficacy of entecavir and lamivudine in the treatment of CHB.

Comparison	Number of study	Pooled OR (95% CI)			Homogeneity			Publication bias	
		OR	95% CI	P	Q value	Ph	I^2 (%)	P for Begg	P for Egger
Virological responses	(8-16)	3.422	2.349-4.985	0.000	20.79	0.008	61.5	0.754	0.287
Biochemical responses	(8-16)	2.173	1.462-3.230	0.000	20.40	0.009	60.8	0.175	0.069
HBeAg clearance	(8, 10, 12-15)	1.127	0.879-1.445	0.345	4.36	0.499	0.0	1.000	0.668
HBeAg seroconversion	(8, 10-12, 14-16)	1.207	0.933-1.562	0.153	8.58	0.199	30.1	0.764	0.368

OR, Odds ratio; CI, confidence interval; Ph, P-value for heterogeneity.

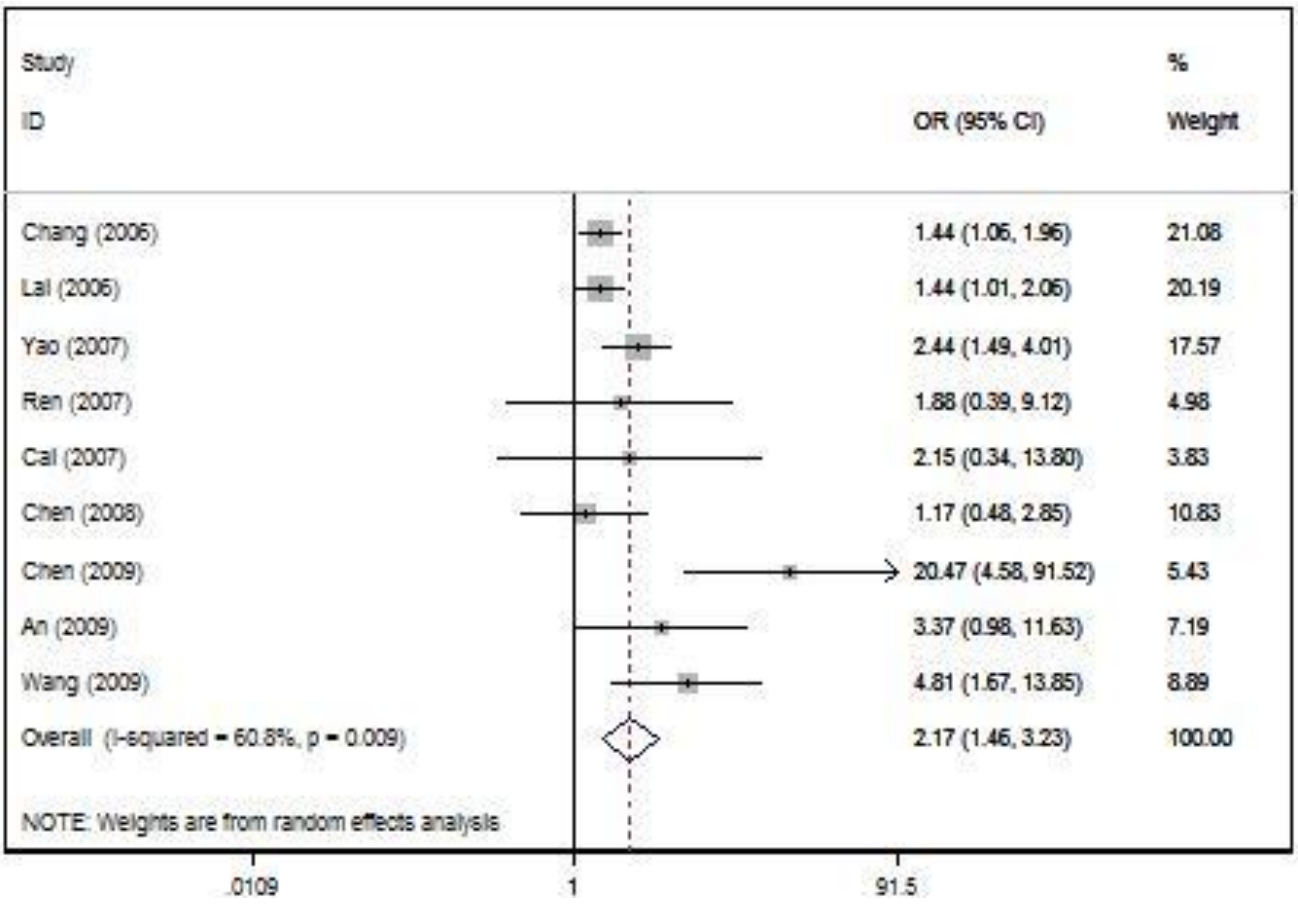

Figure 2. Meta-analysis of the nine trials comparing biochemical responses in ETV and LMV treated patients with chronic hepatitis B after treatment of 48 weeks.

Adverse events

Seven studies (Chang et al., 2006; Lai et al., 2006; Yao et al., 2007; Ren et al., 2007; Cai et al., 2007; An et al., 2009; Wang and Li, 2009) demonstrated incidence of adverse events, however, they were not included in this meta-analysis because the statistical methods and the results of various research were different. No statistically significant differences were observed between cases and controls. The most frequently occurring on-treatment adverse events were nasopharyngitis, increased ALT, upper respiratory tract infection, fatigue, upper- abdominal pain and diarrhea. The number of serious adverse events was not significantly different between the two treatment groups. Few patients discontinued treatment due to adverse events.

Sensitivity analysis

To test the influence of individual dataset on the pooled ORs, we used two methods independently. Firstly, we

deleted small weight studies included in the meta-analysis each time. None of the corresponding pooled ORs was substantially altered by removal of one data set (data not shown). Secondly, trim and fill method was used and pooled ORs were not substantially altered after trim and fill analysis. Both methods indicated that our results were statistically robust.

Heterogeneity

The heterogeneity was reckoned among all studies using the Q statistic (Q > 0.10) and I^2 statistic (I = 0.0%) and heterogeneity was found in virological responses and biochemical responses groups and the random effects model was used.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures and we found no publication bias in this meta-analysis (more details are presented in Table 2).

DISCUSSION

It is now clear that active HBV replication is the key driver of liver injury and disease progression, thus, the aims of treatment of CHB are to achieve sustained suppression of HBV replication and remission of liver disease. The ultimate goal is to prevent cirrhosis, hepatic failure and HCC. Lamivudine is well tolerated on oral administration and has been proven to be highly effective in the treatment of CHB, but the emergence of resistance mutations in the reverse-transcriptase domain of HBV polymerase frequently results in overt viral rebound and disease progression (Allen et al., 1998; Omata et al., 1998; Chang et al., 2004; Liaw et al., 2004). Entecavir, which displayed potent antiviral activity in the woodchuck and duck models of HBV infection (Genovesi et al., 1998; Marion et al., 2002), was approved by the USA food and drug administration in 2005 for the treatment of CHB. The previous study reported that entecavir was superior to lamivudine in reducing viral load and biochemical outcomes in nucleoside-naive patients with CHB infection, but some studies have shown inconsistent response rates. Two multicentre, double-blind and randomized controlled trials demonstrate that virological response rates (66.7 versus 51.6%), biochemical responses rates (68.4 versus 88.9%), clearance and seroconversion of HBeAg (22 versus 18.2%, 20.9 versus 14.7%, respectively) of entecavir for HBeAg-positive CHB were inconsistent, though their criteria of therapeutic effect and biochemical reagent were uniform (Chang et al., 2006; Yao et al., 2007). Similarly, different responses rates of loss of HBV DNA and ALT normalization were reported in others studies, so this meta-analysis was conducted.

Nine literatures were chosen to perform the meta-analysis, it was demonstrated that entecavir better suppressed HBV DNA than lamivudine and the loss of HBV DNA rates were 76.6 and 53.6% (P = 0.000), respectively. Similarly, greater ALT normalization rates were observed for patients given entecavir monotherapy when compared with lamivudine monotherapy groups (80.4 versus 68.3%, P = 0.000). We extracted data of HBeAg-positive CHB patients, but no significant differences were observed between cases and controls for clearance and seroconversion of HBeAg (22.3 versus 19.9%, P = 0.345; 19.9 versus 17.3%, P = 0.153, respectively). The most frequently occurring on-treatment adverse events were nasopharyngitis, increased ALT, upper respiratory tract infection, fatigue, upper- abdominal pain and diarrhea. There were no statistically significant differences observed between cases and control either.

It should be noted that there were some limitations in this meta-analysis study. Firstly, since only published studies were included in the meta-analysis, publication bias may have occurred, even though it was not found by making use of statistical test. Secondly, meta-analysis essentially remained as observational study that was subject to the methodological deficiencies of the included studies. Thirdly, criteria of loss of HBV DNA and biochemical reagent were not uniform in several studies. Another limitation is that this population was not analyzed for the lamivudine resistance genotype, which might explain the lamivudine results.

Long-term monitoring showed low rates of resistance in nucleoside-naïve patients during 5 years of entecavir therapy, rates of phenotypic resistance were 0.2, 0.5, 1.2, 1.2 and 1.2% and rates of virologic breakthrough were 0.2, 0.2, 0.8, 0.8 and 0.8% on 1, 2, 3, 4 and 5 year, respectively (Tenney et al., 2009). While, high rates of resistance in nucleoside-naïve patients during 5 years of lamivudine therapy, rates of phenotypic resistance were 17, 40, 57, 67 and 69% respectively (Chang et al., 2004; Keeffe et al., 2006). These findings supported the selection of entecavir as a primary therapy that enabled prolonged treatment with potent viral suppression and minimal resistance, but we could not conduct this meta-analysis because the studies of comparing the efficacy of entecavir and lamivudine for chronic hepatitis B treatment which exceeded 96 weeks were rare (Gish et al., 2007; Yao et al., 2008; Chang et al., 2008).

In conclusion, our meta-analysis study confirms that entecavir increases the incidence of virological and biochemical responses compared to lamivudine after treatment of 48 weeks.

ACKNOWLEDGEMENTS

This study was supported by a grant from the National Natural Science Foundation of China (30771907), foundation of pre-973 program projects (2009CB526411)

and specialized research fund for the doctoral programme of higher education of China (20093420120005).

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