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ORIGINAL ARTICLE

Lamivudine or lamivudine combined with hepatitis B immunoglobulin in prophylaxis of hepatitis B recurrence after liver transplantation: a meta-analysis

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Keywords
hepatitis B immunoglobulin, hepatitis B virus recurrence, lamivudine, liver transplantation, YMDD mutant.

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Summary

There is a controversy over whether the different outcomes of prophylaxis of hepatitis B virus (HBV) recurrence are attributable to different treatments. A systematic review and a meta-analysis were conducted to evaluate lamivudine monotherapy and combined therapy of lamivudine and hepatitis B immunoglobulin (HBIG) in HBV infected liver recipients. A fixed effects model was used for statistical pooling of relative risks (RR) for the different outcomes. Six articles (551 patients) fulfilled the inclusion criteria. Statistically significant differences were observed between lamivudine monotherapy and lamivudine + HBIG therapy in hepatitis B recurrence [$P < 0.0001$; RR = 0.38; 95% CI (0.25, 0.58)], YMDD mutant [$P = 0.002$; RR = 0.40; 95% CI (0.23, 0.72)] and hepatitis B recurrence in HBV-DNA positive patients before orthotopic liver transplantation [$P < 0.00001$; RR = 0.31; 95% CI (0.21, 0.45)]. No significant differences were observed in patient survival [$P = 0.59$; RR = 1.02; 95% CI (0.95, 1.09)], graft survival [$P = 0.56$; RR = 1.02; 95% CI (0.95, 1.09)] and diseases leading to death between the two groups [HBV recurrence leading to death: $P = 0.05$; RR = 0.47; 95% CI (0.22, 1.02); hepatocellular carcinoma recurrence leading to death: $P = 0.13$; RR = 0.34; 95% CI (0.09, 1.36)]. In conclusion, combination of lamivudine and HBIG can effectively decrease the recurrence rate of HBV and the incidence of YMDD mutant, but it can not improve patient survival and graft survival significantly. Well-designed large-sample trials are needed to evaluate the efficiency of combined therapy of lamivudine and HBIG in prophylaxis of HBV recurrence in liver graft recipients.

Introduction

Recurrence of hepatitis B virus (HBV) infection in liver graft recipients with chronic hepatitis B is universal. Most recipients have a poor graft survival rate if no prophylaxis strategy is prescribed. Prophylaxis of HBV recurrence using either immune or antiviral therapies has achieved encouraging outcomes in the past decades [1–4]. Hepatitis B immunoglobulin (HBIG) was used on earlier occasions to prevent HBV recurrence, while lowering the recurrence rate of HBV from 80% to 20% [5–7]. But long-term administration of HBIG is costly and less efficacious in patients with a high level of viremia before liver transplantation (OLT), which is a contradictory problem in prophylaxis of HBV recurrence after OLT [1]. By changing intravenous to intramuscular injection of HBIG, using different levels of HBIG dosage, combining with HBIG and lamivudine, studies have been carried out to search for a better strategy to prevent HBV recurrence [5,8–10].

Recent studies have found that combined treatment with lamivudine and HBIG can decrease the risk of HBV recurrence and achieve a higher graft survival rate [2–5,11]. Trials reveal that maintenance therapy with

lamivudine after discontinuation of long-term HBIG therapy is associated with a low risk of HBV recurrence after liver transplantation in HBV patients [1,12]. Neff reported that no additional advantage was conferred by combined use of lamivudine and HBIG compared with lamivudine monotherapy in patients negative for HBV DNA before liver transplantation. Yet combination of HBIG and lamivudine appeared to decrease the risk of HBV recurrence in comparison to lamivudine monotherapy for liver recipients positive for HBV DNA before liver transplantation [2,13,14]. However, most studies were limited by small samples or short-term follow-up. Hence, no reliable conclusions have been drawn on whether lamivudine + HBIG therapy is superior to lamivudine monotherapy in prophylaxis of HBV recurrence in liver graft recipients.

This meta-analysis, therefore, aimed to determine whether there are significant differences in HBV recurrence, YMDD mutant, patient and graft survival, and diseases leading to death between lamivudine + HBIG therapy and lamivudine monotherapy.

Patients and methods

Search strategy

We searched the databases EMBASE, MEDLINE, BIOSIS, CINAHL, CNKI and DERWENT until April 2008. In addition, a manual search was conducted of most recent journals including *Gastroenterology, Hepatology, J Hepatol, Liver Transplant, Transplantation, Transplant Proc, Transplant Infect Dis, Am J Transplant, Chin Med J, Zhong Hua Wai Ke Za Zhi, Clin Transplant, Hepatobiliary Pancreat Dis Int. World Chin J Dig* published studies from January 1988 to April 2008 were also reviewed. Key words used in electronic searching included 'HBIG' 'hepatitis B immunoglobulin' 'liver transplantation' and 'lamivudine'.

Selection criteria

Inclusion criteria: (i) trials of case–control or cohort research on prophylaxis of HBV recurrence after liver transplantation with or without HBIG; (ii) randomized groups in these trials; (iii) groups treated with lamivudine + HBIG and control groups with lamivudine monotherapy; (iv) the trials giving definite criteria of HBV recurrence; and (v) allogeneic liver recipients were included, gender, age and nationality were not restricted.

Exclusion criteria: (i) patients treated for other hepatitis, type C or D; (ii) prophylaxis with other treatment using adefovir, entecavir, etc.; and (iii) incomplete data or with limited outcomes.

Trials were not excluded for reason of different languages used. When results from some or all patients in a clinical trial were reported more than once, data on endpoints from the publication with the longest follow-up were extracted.

Data collection and analysis

Two of the investigators (WS, R and XJ, W) reviewed all the reported studies independently. Data were extracted according to clinical and demographic characteristics, duration of follow-up, HBV recurrence, YMDD mutant, patient and graft survival, diseases leading to death [HBV recurrence and hepatocellular carcinoma (HCC) recurrence]. A meta-analysis was also made for these parameters with homogeneity among the different trials.

Methodological quality of trials

Two reviewers (WS, R and XJ, W) assessed the trials independently. Quality examination included sample size computation, methodology for generating random allocation sequence, concealment of allocation, blinding and completeness of follow-up.

Statistical analysis

Dichotomous outcomes were expressed as relative risk (RR) with 95% confidence intervals (CIs). Heterogeneity was analyzed among the trials using the Cochrane Q-test and calculating the I-square index to measure the proportion of total variation attributable to heterogeneity beyond chance. If no heterogeneity was detected, the overall treatment effect size was calculated as a weighted average of the results of each primary study. The results reported herein used the fixed-effect model. All statistical analyses were performed using the Review Manager Software 4.2.

Results

Literature and search

An initial electronic search identified 511 reports (Fig. 1). After the first review, 29 reports were excluded for duplication and 394 reports for either not including data relating to lamivudine or lamivudine + HBIG therapy or not including relative characteristics of HBV recurrence. The number of potentially related clinical trials identified for more detailed evaluation was 88. A total of 81 articles were excluded after the second review because they were not randomized ($n = 49$) or did not provide any information about HBV recurrence ($n = 33$). Therefore, six trials were determined as appropriate to be included in the systematic review (Table 1), and these trials with 551 participants were retrieved by online search (lamivudine:lamivudine + HBIG = 245:306).

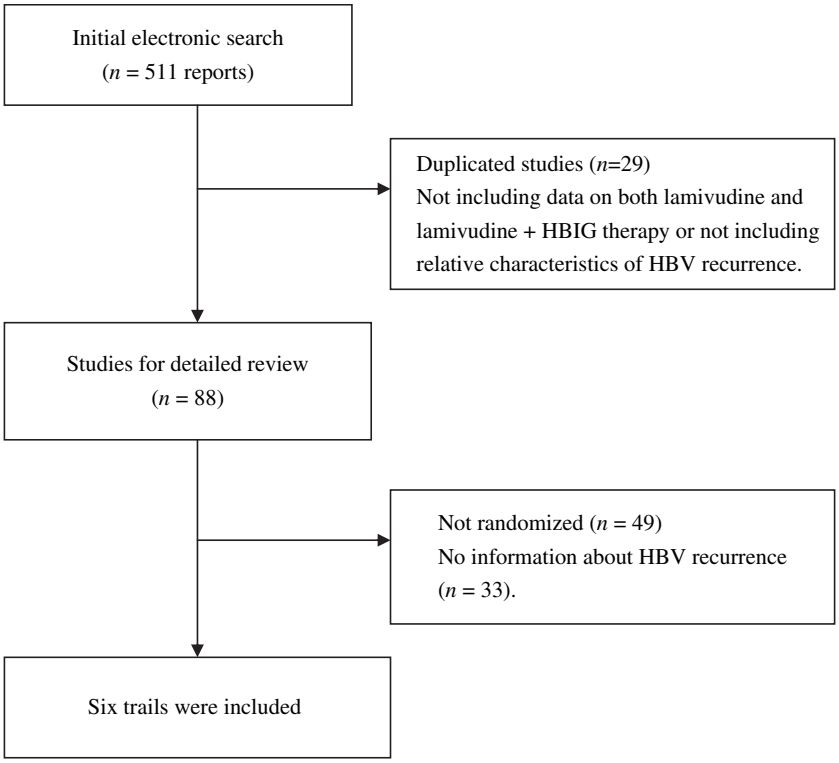

Figure 1 Flowchart describing the procedure for selection of studies. Trials: prophylaxis of HBV recurrence after liver transplantation.

Trials included

Baseline features of the trials included are shown in Table 1. Intramuscular HBIG was found in the six trials. In five trials, lamivudine was used at a dose of 100 mg/day and in another trial at a dose of 150 mg/day. For long-term prophylaxis of HBV recurrence after liver transplantation, HBIG 400–800 IU/month was used in four trials, HBIG of 10 000 IU/month in one and HBIG 2000 IU/month in another.

Quality of included trials

All the six trials were randomized, and one of them had a detailed description of methods for randomization and perspectiveness. All had complete follow-up. Patients covered by four articles had a follow-up of 60–104 months.

Outcomes

Hepatitis B recurrence

Hepatitis B recurrence was reported in all the trials (Fig. 2) and significant differences were observed between the two groups [$P < 0.0001$; RR = 0.38; 95% CI (0.25, 0.58)].

YMDD mutants

YMDD mutants were reported in five trials (Fig. 3). Significant difference was observed in YMDD mutant between the two groups [$P = 0.002$; RR = 0.40; 95% CI (0.23, 0.72)]. Lamivudine + HBIG in prophylaxis of HBV recurrence resulted in fewer YMDD mutants, compared with lamivudine monotherapy.

Patient and graft survival

Patient and graft survivals were found in all trials (Figs 4 and 5) though no significant difference was observed between the two groups [patient survival $P = 0.59$; RR = 1.02; 95% CI (0.95, 1.09); graft survival $P = 0.56$; RR = 1.02; 95% CI (0.95, 1.09)].

Hepatitis B recurrence for HBV-DNA positivity before liver transplantation

Hepatitis B recurrence for HBV-DNA positivity before liver transplantation was reported in five trials (Fig. 6). Significant difference was observed in hepatitis B recurrence in HBV-DNA positive patients before liver transplantation between the two groups [$P < 0.00001$; RR = 0.31; 95% CI (0.21, 0.45)].

Other endpoints

Hepatitis B virus recurrence and HCC recurrence were the two main factors leading to death of liver recipients (Figs 7 and 8). There were no statistically significant difference in the two factors between lamivudine and lamivudine + HBIG therapies [HBV recurrence leading to death: $P = 0.05$; RR = 0.47; 95% CI (0.22, 1.02); HCC

Table 1. Characteristics of trials included in the review.

Study	Unicenter/ multicenter	Double blind?	Prospective/ retrospective	HBV recurrent criteria	Inclusion criteria	Follow up (months)	No. patients	Treatment dosage
Buti *et al.* [15]	Multicenter	No	Prospective	HBsAg(+)/HBV DNA > 10^6 copies/l	HBV DNA < 2.5 pg/ml at time of OLT	83	29	LAM 100 mg/day p.o.; HBIG 2000 IU/month IM
Zheng *et al.* [12]	Unicenter	No	Retrospective	HBsAg positive	Liver failure caused by chronic HBV infection	60	165	LAM 100 mg/day p.o.; HBIG 800 IU/month IM
Neff *et al.* [13]	Multicenter	No	Retrospective	HBsAg positive/HBV-DNA positive	HBsAg positive	104	92	LAM 150 mg/day p.o.; HBIG 10 000 IU/month IM
Zhu *et al.* [16]	Unicenter	No	Retrospective	HBsAg positive/HBV-DNA positive	End-stage liver disease	32	34	LAM 100 mg/day p.o.; HBIG 400–800 IU/month IM
Wu *et al.* [14]	Unicenter	No	Retrospective	HBsAg positive/HBV-DNA positive	HBsAg positive/HBV-DNA positive	18	120	LAM 100 mg/day p.o.; HBIG 400 IU/month IM
Jiao *et al.* [17]	Unicenter	No	Retrospective	HBsAg positive/HBV-DNA positive	HBsAg positive last at least 6 months before OLT	66	111	LAM 100 mg/day p.o.; HBIG 800 IU/month IM

In Buti's trial, patients received HBIG and lamivudine for 1 month and were then randomized to receive the combination therapy or monotherapy.
LAM, lamivudine; HBIG, hepatitis B immune globulin; IM, intramuscular.

recurrence leading to death: $P = 0.13$; RR = 0.34; 95% CI (0.09, 1.36)]. The funnel pilot is symmetry, similar to an invert funnel, which means no much publication bias exists in this meta-analysis (Fig. 9).

Discussion

Hepatitis B virus recurrence in liver transplantation was highly heterogeneous. High virus replication status, low efficiency of antiviral strategy, and HBV YMDD mutant were the main factors for disease progression [2,5,6,11–14]. As shown in this review, combination of lamivudine and HBIG can effectively decrease the recurrence rate of HBV and the incidence of YMDD mutant. Patient and graft survivals tended to be higher after the combination therapy than after lamivudine monotherapy. There is no significant difference between the two therapies. But more patients will die of HBV recurrence after lamivudine monotherapy, than after combination therapy ($P = 0.05$).

Hepatitis B virus-DNA positivity before liver transplantation seems to be more likely to induce HBV recurrence [1,5]. The risk of hepatitis B recurrence after liver transplantation in patients with HBV DNA $>10^5$ copies/ml is significantly higher than that in patients with HBV DNA $<10^5$ copies/ml either after lamivudine monotherapy or combination therapy [5,12,18]. HBV-DNA positivity was detected in fewer liver recipients after lamivudine + HBIG therapy than in those after lamivudine monotherapy (Table 2). Hepatitis B recurrence was significant between the two therapies in HBV-DNA positive patients before liver transplantation ($P < 0.00001$).

Quantitative PCR tests are required to measure the HBV-DNA levels of patients with a low level of viremia so as to decide lamivudine therapy before liver transplantation [9,18,19] from a virologic standpoint, Wong *et al.* [1] postulated that detection of HBV DNA before liver transplantation may precede the reappearance of serum hepatitis B surface antigen (HBsAg). Detectable HBV DNA and negative HBsAg in patients indicate an occult or sub-clinical reinfection. A Michigan trial reported that transient detection of low levels of serum HBV DNA after liver transplantation may not necessarily signify HBV recurrence. But the level of HBV DNA over 5 log copies/ml indicates a high HBV recurrence after liver transplantation [1,16].

Antiviral therapy-resistant mutants may be harbingers of HBV recurrence and may warrant intervention before reappearance of HBsAg in order to prevent hepatitis flares [1,20]. It was reported that before liver transplantation, YMDD mutant selection can pose an increased risk of HBV recurrence, even in patients treated with lamivu-

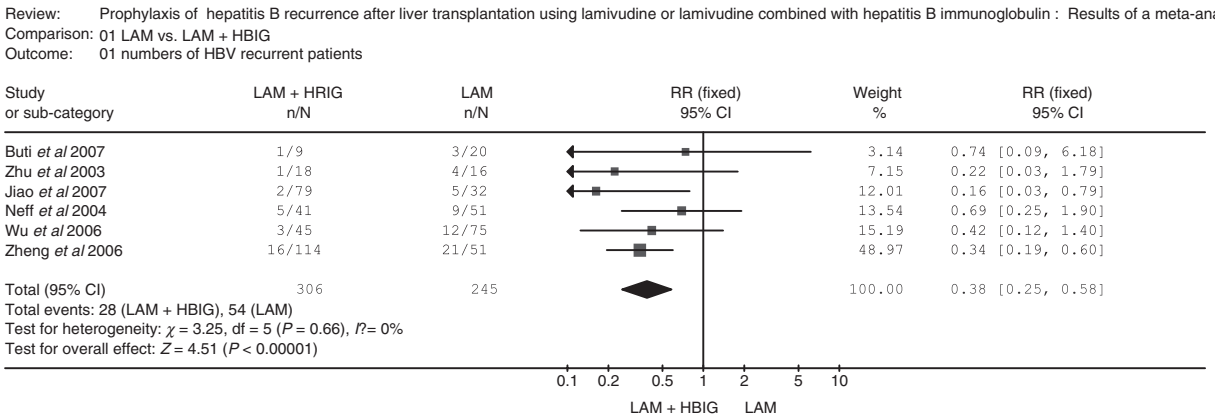

Figure 2 Lamivudine or lamivudine combined with HBIG in prophylaxis of hepatitis B recurrence after liver transplantation: results of a meta-analysis: hepatitis B recurrence.

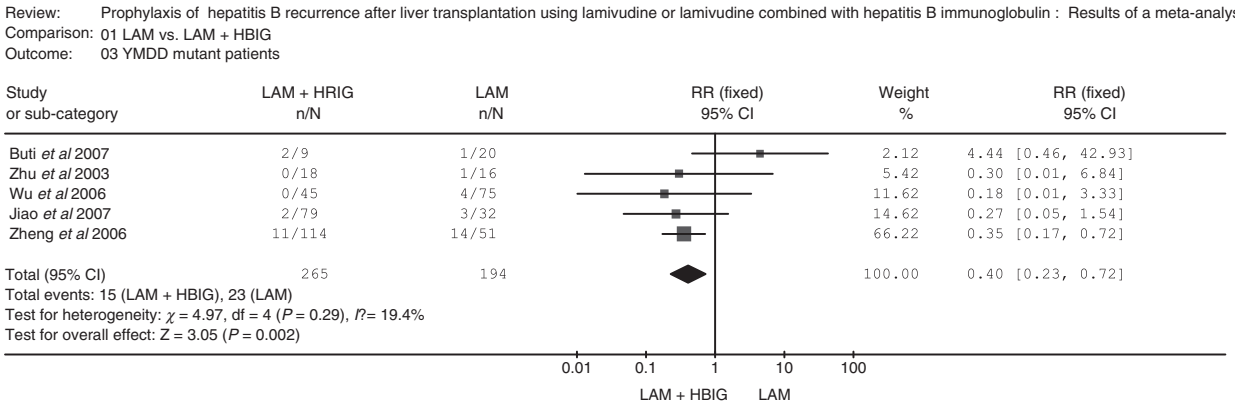

Figure 3 Lamivudine or lamivudine combined with HBIG in prophylaxis of hepatitis B recurrence after liver transplantation: results of a meta-analysis: YMDD mutant.

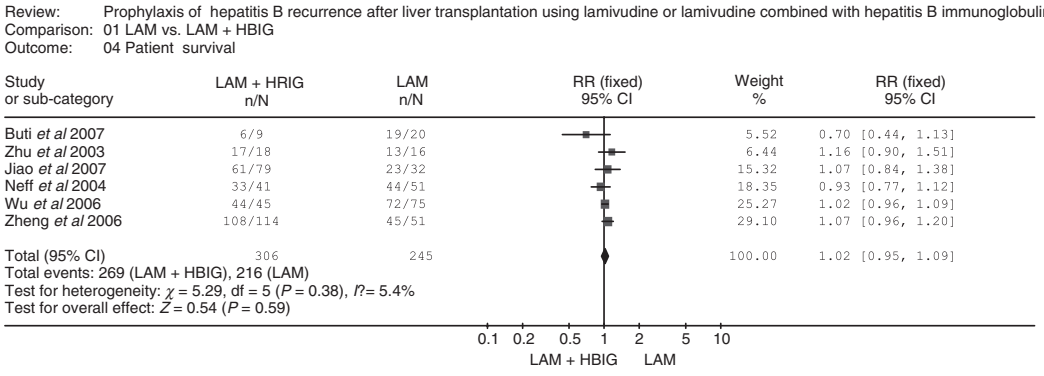

Figure 4 Lamivudine or lamivudine combined with HBIG in prophylaxis of hepatitis B recurrence after liver transplantation: results of a meta-analysis: patient survival.

dine + HBIG [21]. YMDD mutant can be detected in 15–30% of patients after 1-year treatment and in 50% after 3-year treatment [12]. Moreover a high-dose of intravenous HBIG exerts selection pressure over HBV, resulting in the dominance of variant viruses or the escape of mutants [22]. In addition, combination therapy can be

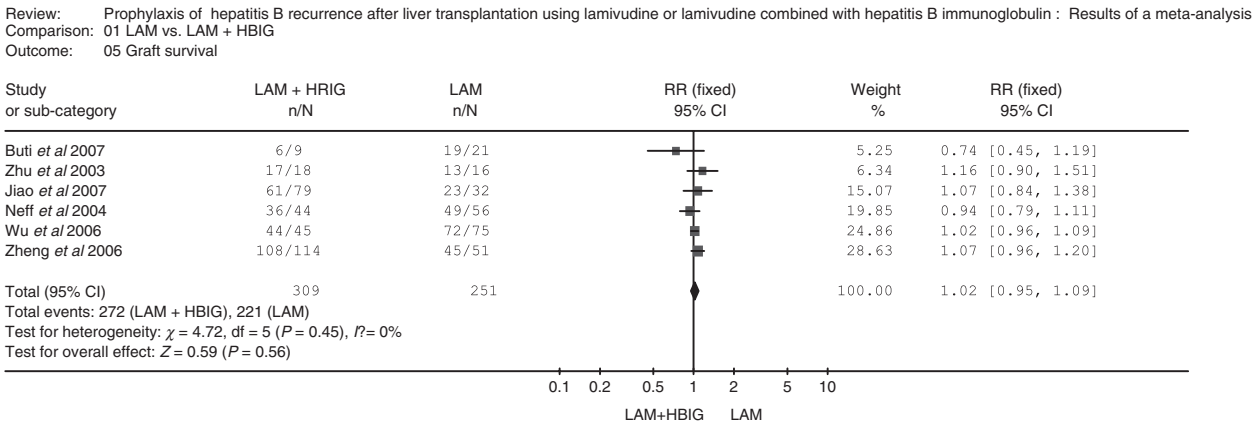

Figure 5 Lamivudine or lamivudine combined with HBIG in prophylaxis of hepatitis B recurrence after liver transplantation: results of a meta-analysis: graft survival.

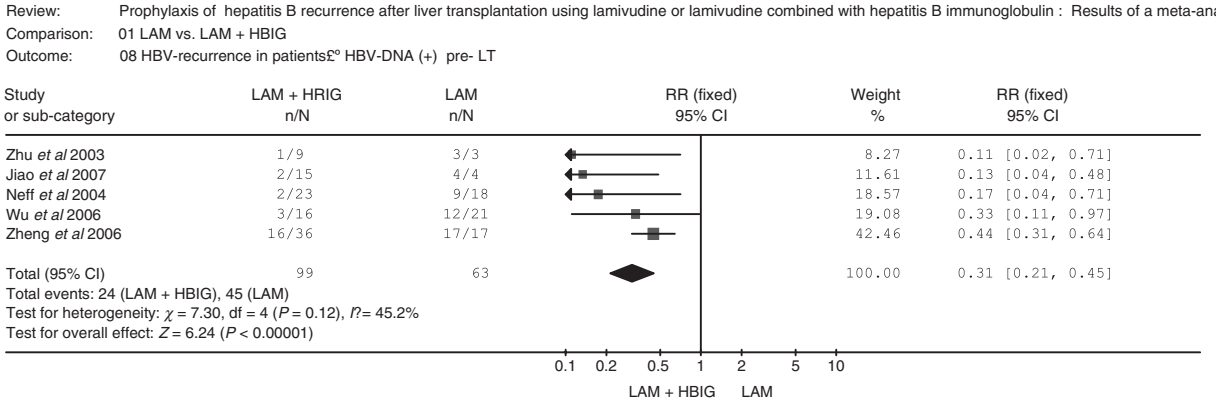

Figure 6 Lamivudine or lamivudine combined with HBIG in prophylaxis of hepatitis B recurrence after liver transplantation (LTx): results of a meta-analysis: HBV-recurrence in patients: HBV-DNA positive pre-LTx.

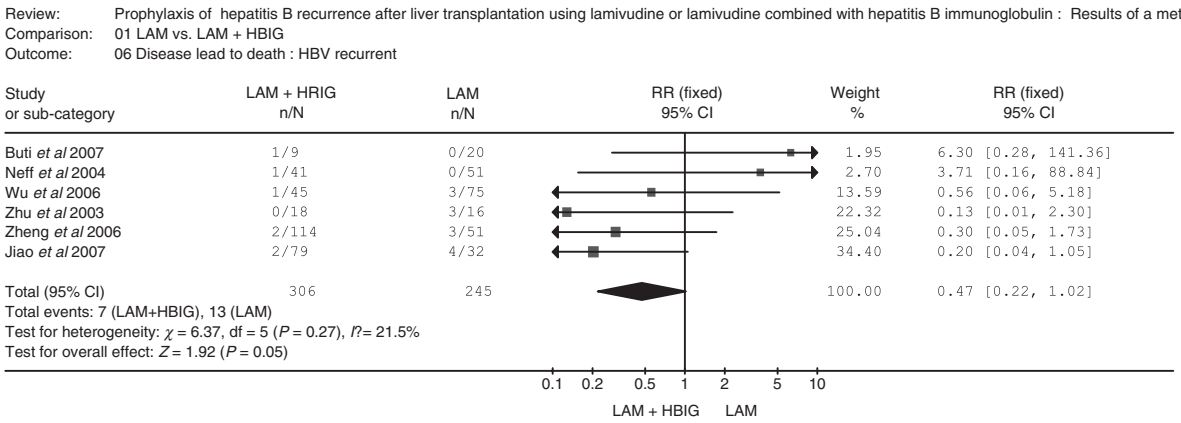

Figure 7 Lamivudine or lamivudine combined with HBIG in prophylaxis of hepatitis B recurrence after liver transplantation: results of a meta-analysis: disease leads to death: HBV recurrence.

cost-effective, as HBIG is more expensive than lamivudine [9,23]. However, no statistical data are available in the six articles we reviewed.

In summary, lamivudine and HBIG are two main agents recommended for prophylaxis of HBV recurrence and YMDD mutant. However, no significant difference

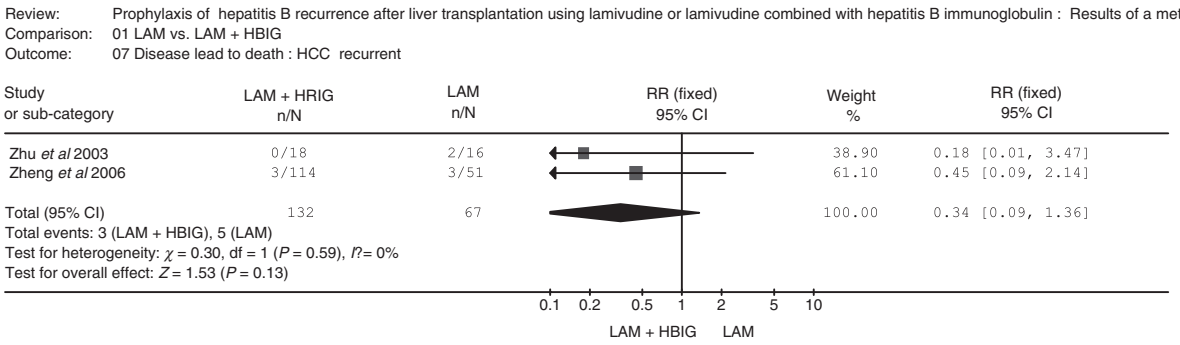

Figure 8 Lamivudine or lamivudine combined with HBIG in prophylaxis of hepatitis B recurrence after liver transplantation: results of a meta-analysis: disease leads to death: HCC recurrence.

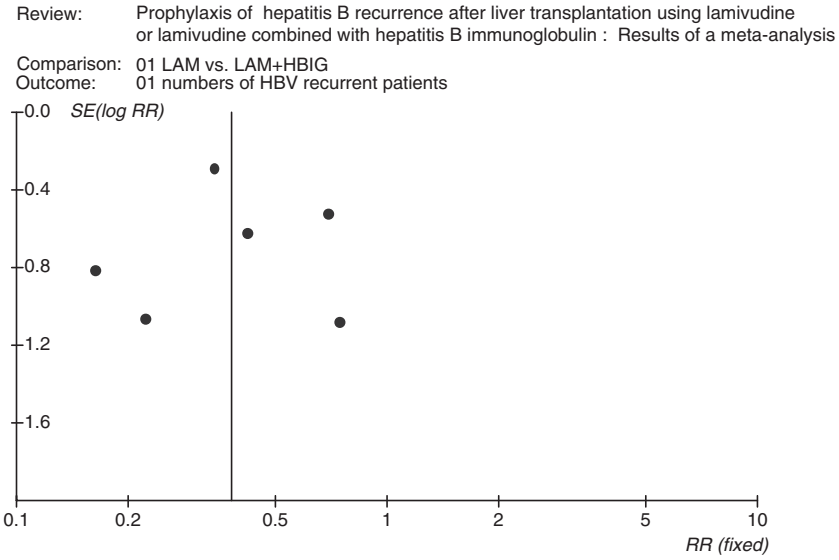

Figure 9 Funnel plot of articles extracted for this meta-analysis.

Table 2. Characteristics of trials included in the review: HBV-DNA positive before and after liver transplantation.

	Pre-LTx		Post-LTx	
Study	LAM	LAM + HBIG	LAM	LAM + HBIG
Buti *et al.* [15]	0/20	0/9	0/20	0/9
Zheng *et al.* [12]	17/51	36/114	15/51	10/114
Neff *et al.* [13]	18/51	23/41	7/51	5/41
Zhu *et al.* [16]	3/16	9/18	4/16	1/18
Wu *et al.* [14]	21/75	16/45	NA	NA
Jiao *et al.* [17]	4/32	15/79	5/32	1/79

LAM, lamivudine; HBIG, hepatitis B immune globulin; LTx, liver transplantation; NA, not available.

was detected between the two therapies with regard to patient and graft survival in this review. As the combination therapy can not improve the survival rate of patients in relation to lamivudine monotherapy, HBIG should not be given at a high dose of 10 000 IU/month, which is commonly used in European countries.

In addition, well-designed large-sample trials are needed to evaluate the efficiency of lamivudine + HBIG therapy in prophylaxis of HBV recurrence in liver recipients.

Authorship

WR: designed & performed research; collected & analyzed the data; and wrote the paper. XW: performed research; collected & analyzed the data; and wrote the paper. DX: designed & performed research; contributed important reagents; and wrote the paper.

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