Original Article

Network meta-analysis on prophylactic regimens against recurrent hepatitis B virus infection after liver transplantation

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Background: Previous meta-analyses of non-randomized studies suggested that the hepatitis B immunoglobulin (HBIG) and lamivudine (LAM) combination therapy was significantly better than HBIG or LAM alone in preventing hepatitis B virus (HBV) recurrence after transplantation. However, substantial evidences supporting the superiority of combination therapy are still insufficient. Therefore, we sought to conduct a multiple-treatment comparison to integrate current data which was based on randomized controlled trials (RCTs).

Methods: We searched electronic databases of PubMed, Embase and the Cochrane Library for eligible literatures. Pair-wise meta-analyses were to synthesize studies comparing the same pair of treatments. Appropriate networks for overall and 1-year recurrence rates were established. Bayesian algorithm was used in multiple-treatment comparisons to compare relative effects of all included regimens.

Results: Four RCTs on prophylaxis against HBV recurrence after liver transplantation, involving 162 participants, were included. HBIG mono-therapy, LAM mono-therapy and HBIG plus LAM showed no statistically difference in risk ratios (RRs) in terms of overall HBV recurrence rate in network meta-analysis. Nevertheless, HBIG mono-therapy had potential advantage compared with combination of HBIG and LAM in 1-year HBV recurrence rate [RR 0.00, 95% confidence interval (CI): 0.00 to 0.91] while the rest comparisons revealed no significance. The cumulative probabilities of treatments associated with the highest recurrence were (overall HBV recurrence rate, 1-year HBV recurrence rate): HBIG (18%, 1%), LAM (32%, 42%) and HBIG plus LAM (50%, 57%).

Conclusions: This network meta-analysis based on data from RCTs showed no significant differences among HBIG mono-therapy, LAM mono-therapy, combination of HBIG and LAM in overall HBV recurrence rate after liver transplantation. Further well designed and large-scale RCTs are warranted to clarify these issues.

Keywords: Hepatitis B; liver transplantation; hepatitis B immunoglobulin (HBIG); lamivudine (LAM); network meta-analysis

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Introduction

Chronic hepatitis B virus (HBV) infection, affecting about 400 million people worldwide, is a leading cause of liver-related morbidity and mortality (1,2). It may cause hepatic cirrhosis, liver failure, and hepatocellular carcinoma (HCC) (3). Liver transplantation is the only option for those presenting with end-stage liver disease. However, recurrent HBV infection is common in liver graft recipients with chronic hepatitis B before the availability of immunoprophylaxis (Hepatitis B immunoglobulin, HBIG) and antiviral agents (lamivudine, LAM; adefovir, ADV) (4).

HBIG was firstly utilized to prevent post-transplant recurrence of hepatitis in 1978 (5). Previous study reported substitution of HBIG with LAM was effective for prevention of HBV recurrence in low-risk liver transplant recipients (6). Systematic review has already highlighted that combination treatment with HBIG and LAM reduced HBV recurrence following liver transplantation, compared with HBIG or LAM alone, whereas the included studies were all non-randomized (7). Latest clinical research showed combination of ADV with LAM could provide equivalent protection against recurrent HBV infection, compared with HBIG plus LAM prophylaxis (8). However, the relative effects of current regimens in prophylaxis against HBV recurrence based on irrefutably evidences of are still to be studied.

Network meta-analysis, also known as multiple-treatments comparison, enables us to synthesize data from both direct (within-trial comparisons) and indirect comparisons (inter-trial treatment comparisons through a common comparator treatment) of diverse regimens (9,10). We aimed to provide a clinically useful summary of the results from network meta-analysis that compared all the currently available treatments for preventing post-liver transplantation hepatitis B recurrence.

Materials and methods

Study searching

All relevant articles were retrieved from PubMed, Embase and the Central Registry of Controlled Trials of the Cochrane Library using a combination of the terms "liver transplantation", "Hepatitis B virus", "HBV", "hepatitis B immunoglobulin", "HBIG" and "lamivudine". An additional search through Google Scholar and a manual search through published literature were additionally performed. Two authors (ZY and KS) searched independently. There was no restriction of language or year.

Inclusion and exclusion criteria

Eligible studies included: (I) randomized controlled trials (RCTs) on prophylaxis against HBV recurrence after liver transplantation, studying patients with HBV-related disease; (II) prophylaxis with HBIG mono-therapy, antivirals, or both for prevention of recurrent HBV infection; (III) integrated description of methods and baseline characteristics; (IV) the trials giving definite criteria of HBV recurrence and recurrence rates; (V) allogeneic liver recipients were included, gender, age and nationality were not restricted.

The following exclusion criteria were used: (I) case series, case reports, reviews and conference reports; (II) studies lacking a control group; (III) studies that were unable to provide clear baseline characteristics; (IV) patients treated for other hepatitis virus related diseases, such as type C or D.

Outcomes

The outcomes measured were recurrence rates within the first year and the rates throughout the whole follow-up. Recurrence of HBV infection was denoted as reappearance of hepatitis B surface antigen (HBsAg) in the serum after transplantation. The recurrent events were counted from the randomization.

Data extraction and quality assessment

Two reviewers (FW and WX) independently selected the studies and extracted data following inclusion and exclusion criteria. Data discrepancies between the two reviewers were discussed by the two investigators to reach consensus. Authors of included studies were contacted when clarification was needed. Other two reviewers (ZY and KS) assessed the trials independently. The methodological quality of included randomized clinical studies was assessed using the Jadad scale (11), including generation of the allocation sequence, double blinding and follow-up (*Table 1*). All of the included studies were of high quality.

Statistical analysis

First, we conducted pair-wise meta-analyses with a random-effects model to synthesize studies comparing the same pair of treatments. The results were reported as pooled risk ratio

Table 1 Methodological quality of included randomized clinical studies were assessed using the Jadad scale

Lead author [y]	Generation of the allocation sequence[1]	Double blinding[2]	Follow-up[3]	Total points/rank[4]
Peter W, Angus [2008] (8)	2	0	1	3/High
María Buti [2003] (12)	2	0	1	3/High
María Buti [2007] (13)	2	0	1	3/High
S. J. Park [2002] (14)	2	0	1	3/High
K. W. Lee [2001] (15)	2	0	1	3/High
Nikolai V. Naoumov [2001] (6)	2	0	1	3/High

[1], Generation of the allocation sequence (2 points, computer-generated random numbers or similar; 1 point, not described; 0 points, non-randomization or inadequate method); [2], Double blinding (2 points, identical placebo tablets or similar; 1point, not described; 0 points, no blinding or inadequate method; [3], Follow-up (1 point, number and reasons for dropouts and withdrawals described; 0 points, number or reasons for dropouts and withdrawals not described); [4], The quality score was ranked as low (≤2 points) or high (≥3 points).

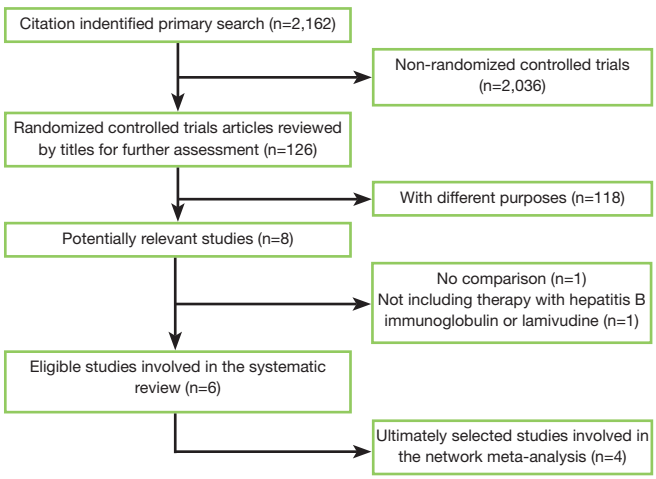

Figure 1 Profile summarizing the trial flow.

(RR) with the corresponding 95% confidence interval (CI). Statistical heterogeneity across studies was assessed with a forest plot and the inconsistency statistic (I^2). Statistical significance was regarded as P<0.05. All calculations were performed using REVIEW MANAGER (version 5.0 for Windows; the Cochrane Collaboration, Oxford, UK).

Second, we built a random-effects network within a Bayesian framework using Markov chain Monte Carlo methods in ADDIS 1.15 (Drugis.org) (16). We networked the translated binary outcomes of HBV recurrence rates within studies and specified the relations among the RRs across studies making different comparisons as previously reported (17), with which, direct and indirect evidences for any given pair of treatments were combined. We used P<0.05 and 95% CIs beyond the null value to assess significance.

We also estimated the probability of each treatment being as the best regimen, the second best, the third best and so on, by calculating the RR of each treatment group compared with arbitrary common controls, and counting the proportion of iterations of the Markov chain of the RR ranking in treatments. We ranked treatments in terms of the risk of HBV recurrence with the same methods.

A variance calculation and a node-splitting analysis provided by the software ADDIS 1.15 were applied to evaluate the inconsistency within the network meta-analysis. Significant inconsistency existed if the difference between random effects variance and inconsistency variance was large or a P<0.05 of disagreement between direct and indirect evidences was met. We would adjust the study included and ultimately obtain an ideal network with consistency according to quantitative estimation.

Results

Eligible studies

We identified 2,162 records according to the search strategy and finally included six RCTs that compared HBIG, LAM, ADV or their combinations in prophylaxis of HBV recurrence after liver transplantation for HBV related diseases (6,8,12-15). *Figure 1* was flow chart. However, we excluded the studies by Naoumov *et al.* (6) and Angus *et al.* (8) due to long-term post-transplantation treatments of HBIG before randomization. A total of 162 patients from four ultimately selected RCTs were involved. There were 50, 58 and 54 patients allocated to HBIG mono-therapy,

LAM mono-therapy and HBIG in combination with LAM, respectively. The range of median follow-up was 17.1 to 83 months among included studies. The enrollment of patients in Buti's studies was basically with no overlap between 2007 and 2003 (12,13). Notably, all of our included RCTs didn't show significant difference in pairs. *Table 2* summarized the characteristics of all involved studies.

Direct meta-analysis

In terms of overall HBV recurrence rate after liver transplantation, we found combination of HBIG and LAM showed comparable efficacy of prevention with LAM mono-therapy by Buti's studies with an RR of 2.00 (95% CI: 0.34 to 11.83; P=0.44) and included studies of HBV recurrence rate were homogeneous (Chi^2 =0.43, P=0.51, I^2 =0%) (12,13). The two groups represented similar outcomes in recurrence within one year after randomization (RR 0.93, 95% CI: 0.12 to 7.08; P=0.44; heterogeneity: Chi^2 =0.00, P=1.00, I^2 =0%).

Network meta-analyses for the risk of HBV recurrence

We established a network for comparisons of HBIG mono-therapy, LAM mono-therapy and combination therapy of HBIG and LAM (see *Figure 2*). *Figure 3* summarized the results of the network meta-analyses regarding HBV recurrence rates. According to the results, HBIG mono-therapy, LAM mono-therapy and HBIG plus LAM showed no statistically difference in RRs in terms of overall HBV recurrence rates. Nevertheless, HBIG mono-therapy had potential advantage compared with combination of HBIG and LAM in terms of 1-year HBV recurrence rate (RR 0.00, 95% CI: 0.00 to 0.91). The rest comparisons revealed no significance in 1-year HBV recurrence rate.

Rank probabilities

Figure 4 shows the treatment ranking of probability to be the worst treatment. Agents with greater value of the histogram were associated with greater probabilities for the highest HBV recurrence rate. Based on network, the cumulative probabilities of treatments being associated with the highest recurrence were (overall HBV recurrence rate, 1-year HBV recurrence rate): HBIG (18%, 1%), LAM (32%, 42%) and HBIG combined with LAM (50%, 57%). In other words, for both overall and 1-year recurrence rates, HBIG mono-therapy was the most likely to have the best prophylaxis efficacy, followed by LAM mono-therapy, combination of LAM and HBIG, sequentially.

Discussion

Previous meta-analyses indicated that the HBIG and LAM combination therapy was significantly better than single HBIG or LAM for preventing HBV recurrence after transplantation (7,18,19). However, all these meta-analyses were based on predominantly retrospective non-randomized studies in which patient selection bias existed. For instance, most of these retrospective studies used historical controls with poor comparability (18,19). The true relative effect of combination group versus mono-therapy might be confounded by other factors, which lead to artefact that combination of LAM and HBIG is superior to single agent administration. RCTs could minimize the confounding impact, implying the most objective comparison. The results from this purely RCTs based network meta-analysis were inconsistent with previous views. Our results showed no significant differences in overall HBV recurrence rate after liver transplantation among HBIG mono-therapy, LAM mono-therapy, HBIG combined with LAM, but revealed decreasing potential advantage sequentially. Besides, we found similar results between all the regimens in terms of 1-year HBV recurrence rate, and even significant benefits in HBIG mono-therapy compared with combination of HBIG and LAM. In addition, rank probabilities revealed incidences of HBV recurrence in HBIG mono-therapy, LAM mono-therapy and HBIG combined with LAM were ranged from low to high.

Mechanically, HBIG neutralizes circulating virus particles and induces lysis of infected hepatocytes (20), while antivirals directly reduce viral load at intrahepatic and extrahepatic sites (21). Previous studies showed decreasing virions by HBIG reduced the viral substrate for antivirals, and reduced the occurrence of drug-resistant mutants (22). While lowering viral load caused by antivirals might inhibit the saturation of HBIG binding sites and decrease the immune pressure, leading to emergence of surface antigen mutations (7). Unfortunately, mutations in the surface gene may cause changes in the polymerase gene and vice versa because of overlapping reading frames in HBV genome. As a result, the use of combination treatment may lead to selection of mutations that reduce the efficacy of each of the drugs, therefore causing HBV recurrence (7). Based on our results and the evidences above, we thought HBIG mono-therapy might be critical for early treatment

Table 2 Characteristics of included studies

Lead author [y]	Country of origin	Study arm	Primary liver disease	Comparison and interventions	Age, median (range)/ mean [y]	Gender (male/ female)	HBV DNA positive in total at the baseline	Median follow-up [range][m]	Overall recurrence case in total and (rate, %)	1-year recurrence case in total and (rate, %)	Conclusions
María Buti [2003] (12)	Spain	HBIG + LAM	End-stage HBsAg-positive cirrhosis	10,000 IU HBIG in anhepatic stage and the first day, followed by 5,000 IU in until day 7, then every 2 weeks, then then 4,000 IU weekly until the end of the first month. HBIG was continued for patients in the combination group, 2,000 IU monthly intramuscularly until month 18. LAM 100 mg orally daily	51.1±7.6	14/1	0/15	18	0/15 (0)	0/15 (0)	NS
		LAM		The same dose of HBIG was given only during the anhepatic phase in anhepatic stage and postoperative days until the end of the first month. LAM 100 mg orally daily*	54.4±8.6	13/1	0/14		0/14 (0)	0/14 (0)	
S. J. Park [2002] (14)	Korea	HBIG	HBV infection	10,000 IU of HBIG in anhepatic phase, 10,000 IU daily for the first 6 postoperative days, 10,000 IU weekly for the first month, and then 10,000 IU monthly for the first year	43.3±10.3	24/7	18/31	17.1 [4.0-48.2]	1/31 (3.2)	0/31 (0)	NS
		LAM		Oral LAM 100 mg/day, The same dose of HBIG was given only during the anhepatic phase and for the first 6 consecutive days after liver transplantation*	45.6±10.6	23/7	16/30		3/30 (10.0)	1/30 (3.3)	
K. W. Lee [2001] (15)	Korea	HBIG	HBV infection	10,000 IU of HBIG in anhepatic phase, 10,000 IU daily for the first 6 postoperative days, 10,000 IU weekly for the first month, and then 10,000 IU monthly for the first year	45.6 [19-61]	34/9	13/19	29.8 [6-61]	3/19 (15.8)	0/19 (0)	NS
		HBIG + LAM		Oral LAM 100-150 mg/day at least for 4 weeks preoperatively, then HBIG intravenously during anhepatic phase and daily for the first 6 postoperative days. LAM restarted on the fifth postoperative day, overlapped with HBIG, and given daily for the rest of life			6/24	34 [12-55]	3/24 (12.5)	1/24 (4.2)	
María Buti [2007] (13)	Spain	HBIG + LAM	HBV-associated liver disease	1-month course of HBIG and LAM and then HBIG 2,000 IU/month+ LAM 100 mg/day	48.56±7.9	8/1	0/9	83 [24-100]	3/15 (20.0)#	0/15 (0)#	NS
		LAM		14 patients received only 1-month course of HBIG and LAM (a total of 129,000 IU HBIG per patient) in addition to 100 mg/day of LAM*, while 6 patients received 18 months of HBIG (a total of 163,000 IU per patient) besides 100 mg/day of LAM#	55.35±7.2	19/1	0/20		1/14 (7.1)#	0/14 (0)#	
Peter W. Angus [2008] (8)	Australia, New Zealand	ADV + LAM	HBV-related disease	Low-dose IM HBIG and LAM at least 12 months, then ADV 10 mg/day and LAM 100 mg/day	55 [26-67]	13/3	3/15	21.1 [9.4-35.9]	0/15 (0)	0/15 (0%)	NS
		HBIG + LAM		Low-dose IM HBIG and LAM at least12 months, then continue their current prophylaxis with low-dose (800 IU/month) IMHBIG and LAM 100 mg/day.	51.9 [37-69]	15/3	4/18	21.8 [13.5-35.6]	0/18 (0)	0/18 (0)	
Nikolai V. Naoumov [2001] (6)	UK	HBIG	End stage HBsAg-positive cirrhosis	Received immunoprophylaxis with HBIG for at least 6 months after the operation, then continuous HBIG administration to maintain serum anti-HBs level above 100 IU/L	51 [32-57]	10/2	4/12	12	1/12 (8.3)	1/12 (8.3)	NS
		LAM		Received immunoprophylaxis with HBIG for at least 6 months after the operation, then LAM 100 mg/day	46 [30-61]	11/1	4/12		2/12 (16.7)	2/12 (16.7)	

*, We considered LAM combined with 1 month or 1 week HBIG as LAM mono-therapy; #, Six patients received 18 months of HBIG (a total of 163,000 IU per patient) besides 100 mg/day of LAM were regarded as combination group and their recurrence outcomes were recalculated. Abbreviations: ADV, adefovir; LAM, lamivudine; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; IM, intra-muscular; IU, international unit; HBV, hepatitis B virus; NS, not significant.

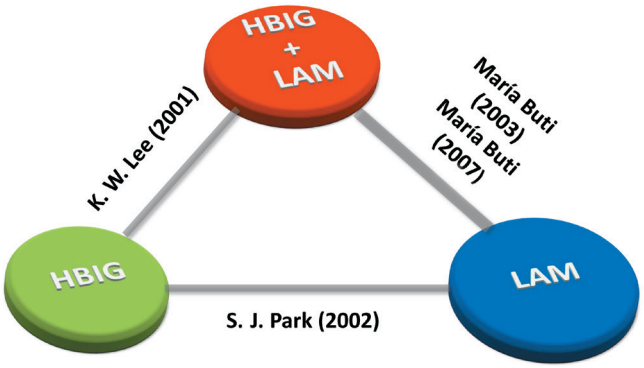

Figure 2 Network established for multiple-treatment comparisons. Solid lines between drugs represented the existence of direct comparisons. Abbreviations: LAM, lamivudine; HBIG, hepatitis B immunoglobulin.

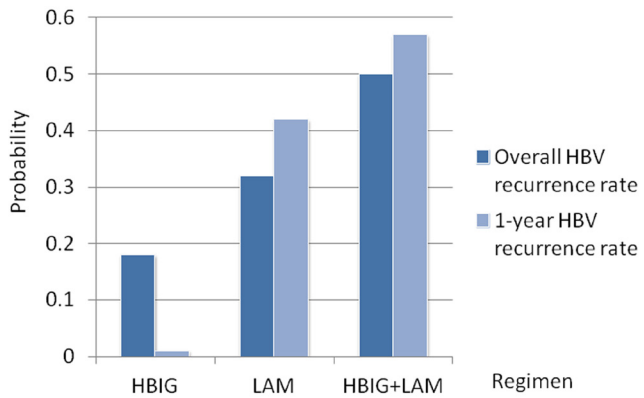

Figure 4 Distribution of probabilities of each therapeutic regimen ranked the first place (highest recurrence) based on network in terms of overall or 1-year HBV recurrence rate. Abbreviations: HBV, hepatitis B virus; HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

instead of combination therapy in prophylaxis of HBV recurrence after liver transplantation. LAM might be more sensitive if viral load was heavier and should be chosen as a replacement therapy when HBIG was not effective. Untimely combination of HBIG and LAM might be prone to drug resistance. In addition, as intravenous injection of HBIG is more expensive and less convenient than LAM, inflexible usage of combination therapy can be less cost-effective (23). Whether combination therapy should be the first choice is debatable. Which therapeutic regimen should be chosen timely that can show superiority in preventing HBV recurrence after liver transplantation is still worthy of further research.

(A) Overall HBV recurrence rate		
HBIG	1.68 (0.27, 11.15)	1.27 (0.18, 9.67)
0.59 (0.09, 3.69)	HBIG+LAM	0.76 (0.09, 5.42)
0.79 (0.10, 5.54)	1.31 (0.18, 10.68)	LAM
(B) 1-year HBV recurrence rate		
HBIG	14583.83 (1.10,6.94E+12)	2878.56 (0.21,5.73E+11)
0.00 (0.00, 0.91)	HBIG+LAM	0.20 (0.00, 5.91E+08)
0.00 (0.00, 4.82)	4.97 (0.00, 9.91E+08)	LAM

Figure 3 Multiple-treatment comparisons for overall or 1-year HBV recurrence rate after liver transplantation based on network. Abbreviations: HBV, hepatitis B virus; HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

This is the first multiple-treatment comparison for the currently available methods in prophylaxis of post-liver transplantation HBV recurrence based on evidences with good quality, which argued with the present consensus of combining LAM and HBIG. However, there existed several limitations. First, the number and sample size of the included studies were still inadequate to draw substantial conclusion. Second, different lengths of median follow-up among the included trials might lead to heterogeneity of outcomes. Third, we failed to evaluate some important clinical outcomes including patient survival and adverse reaction of agents in the current study since these data were reported by few included trials. Therefore, future large sample sized RCTs which would optimize the network and multiple-treatment comparison based on detailed clinical outcomes are warranted to further clarify our assumption. Novel anti-HBV agents such as entecavir, telbivudine or tenofovir were expected to be included.

In conclusion, this network meta-analysis showed no significant differences among HBIG mono-therapy, LAM mono-therapy, combination of HBIG and LAM in overall HBV recurrence rate after liver transplantation.

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