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Hepatitis B Immunoglobulin and Lamivudine Improve Hepatitis B–Related Outcomes After Liver Transplantation: Meta-Analysis

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Abstract

Background & Aims—HBV recurrence increases morbidity and mortality in HBsAg+ patients undergoing liver transplantation. We aimed to estimate the relative efficacy of combined therapy with hepatitis B immunoglobulin (HBIG) and lamivudine (LAM) versus HBIG monotherapy for preventing HBV-related morbidity and mortality in this setting.

Methods—We performed a meta-analysis of clinical trials that met the prespecified criteria and provided data for risk estimation of HBV recurrence in HBsAg+ liver transplant patients receiving HBIG and LAM versus HBIG alone. Databases searched until May 2007 included MEDLINE (Ovid), PubMed, Embase, Toxnet, Scopus, and Web of Science. Literature search and data extraction were conducted independently by 2 study investigators; then 2 other investigators reviewed and screened eligible studies. Odds ratios (ORs) for the risk reduction with HBIG and LAM versus HBIG alone were calculated by using a random-effects model.

Results—Two prospective and 4 retrospective studies were included in the meta-analysis. The OR showing risk reduction in HBV recurrence with HBIG and LAM (n = 193) versus HBIG alone (n = 124) was 0.08 (95% confidence interval [CI], 0.03–0.21). HBV-related death and all-cause mortality could only be assessed in 3 studies each. The ORs showing HBV-related death and all-cause mortality reduction with HBIG and LAM versus HBIG alone were 0.08 (95% CI, 0.02–0.33) and 0.02 (95% CI, 0.06–0.82), respectively.

Conclusions—Although this meta-analysis was limited by small studies and varying levels of immunosuppression, it is apparent that adding LAM to HBIG improved HBV-related morbidity and mortality in HBsAg+ recipients of liver transplants.

HBV infection is a leading cause of liver-related morbidity and mortality worldwide.¹ It is estimated that one third of the world population might be exposed to HBV, making it a major public health problem, especially in Asia, Africa, the Middle East, and parts of Eastern Europe and South America. In the United States approximately 1.25 million individuals are infected with HBV.² Chronic hepatitis B infection might lead to progressive liver disease, cirrhosis,

and liver cancer in a subset of patients that might necessitate liver transplantation to prevent premature mortality.³

Successful management of HBV-infected liver transplant recipients requires effective control of HBV replication after transplantation.⁴ For the prevention of graft rejection, immunosuppressive therapy is needed in the post-transplant setting. HBV is thought to be under immunologic control, and immunosuppression can precipitate recurrence of HBV that might lead to morbidity and mortality in HBsAg+ liver transplant patients.⁴ Initial reports of liver transplantation in HBV-infected patients had dismal results as a result of early HBV recurrence leading to graft loss and mortality.^{5,6} A delicate balance is required between anti-HBV and post-transplant immunosuppressive therapies. In the post-transplant setting, lamivudine (LAM) monotherapy might not be sufficient to prevent HBV recurrence because of the development of LAM resistance.⁷ To suppress HBV recurrence after liver transplant, hepatitis B immunoglobulin (HBIG), LAM, or a combination of HBIG and LAM have been used. The use of HBIG and LAM in post-liver transplant treatment regimens revolutionized the post-transplantation management of HBV and greatly improved HBV-related morbidity after transplantation.⁸

HBIG and LAM are both considered to be safe and effective agents for the treatment of chronic hepatitis B in the post-liver transplant setting.⁸ HBIG is a plasma product that is rich in immunoglobulins that can prevent HBV if given within 14 days of exposure to an HBV-infected individual and is effective in 85%–90% of cases when it is used as a post-exposure prophylaxis. These beneficial effects of HBIG were also used in the post-liver transplant setting to minimize the risk of HBV recurrence. LAM is a potent inhibitor of HBV polymerase and controls HBV effectively.⁹ A greater efficacy of a combination regimen comprising HBIG and LAM rather than HBIG or LAM monotherapy has been reported, suggesting that both immunologic and antiviral therapy are needed for effective control of HBV.¹⁰

Although several small studies have shown a beneficial effect of HBIG and LAM in preventing HBV-related morbidity, the mortality benefits are not apparent because of the small number of patients in individual studies. Furthermore, despite important clinical and health policy implications, the degree of beneficial effects of HBIG and LAM combination therapy in the post-liver transplant setting has not been quantified previously. This prompted us to conduct a meta-analysis to answer the following questions: Is combination of HBIG and LAM better than HBIG alone in reducing the risk of HBV recurrence, HBV-related death, and all-cause mortality in HBsAg+ patients receiving liver transplants, and if so, how much better is the combination therapy versus HBIG alone?

Methods

Search Strategy and Selection Criteria

The following databases were searched in all languages until May 2007: MEDLINE (Ovid), PubMed, Embase, Toxnet, Scopus, and Web of Science, by using the indexing terms of *hepatitis B virus or HBV* in combination with *recurrence or recurrence post-transplantation, or acute hepatic failure post-transplantation or lamivudine or HBIG, or liver or liver transplantation*. In addition, a manual review of the bibliographies of seminal primary and review articles was performed to identify potentially relevant additional studies.

The following criteria were used for study eligibility in the meta-analysis: (1) controlled clinical trials or either retrospective or prospective cohort studies with a control (or a historic control) group that allow assessment of rate of recurrence of hepatitis B after transplantation in patients receiving HBIG and LAM combination therapy (HBIG and LAM) versus HBIG alone; (2) well-defined clinical outcomes defined by reporting at least one of the following: HBV

recurrence or HBV-related death; (3) clear definition of baseline population regarding HBsAg + status; and (4) studies with >5 participants per treatment arm.

Exclusion criteria included lack of (1) extractability of relevant data, (2) interdependence with other trials used in the meta-analysis, or (3) peer review (eg, meeting abstracts). In addition, case reports or series and studies that included rheumatologic diseases and human immunodeficiency virus, transplants other than the liver, and cancer chemotherapy patients were excluded.

Outcomes

Hepatitis B recurrence, defined as the reappearance of HBsAg (with or without HBV DNA positivity) after transplantation according to the authors' report, was the primary outcome. HBV-related death, defined as death occurring after liver transplantation and attributed by the authors to HBV in the absence of other apparent cause of death, and all-cause mortality were included as secondary outcomes.

Meta-analysis

The cumulative rate of each outcome of interest was calculated in both the combination therapy (HBIG and LAM) and HBIG monotherapy arms, standardized by the total sample sizes in each trial. Many of the trials reported few primary and secondary events. Therefore, the odds ratios (ORs) and 95% confidence intervals (CIs) of the outcomes of interest between HBIG and LAM and HBIG monotherapy were calculated with the Peto method.^{11,12} Assuming documented and undocumented differences between studies (eg, immunosuppression regimens), the summary (pooled) ORs were estimated by using a random-effects model. As confirmation for the stratified OR estimates, *P* values, and confidence limits, exact stratified methods with STATXACT software, version 6 (Cytel Inc, Cambridge, MA) were also computed. Analysis of heterogeneity across studies was performed with a Cochran Q statistic as described previously¹³ and confirmed with the test of Breslow and Day.¹⁴ Publication bias within studies was examined visually by funnel plots and then analyzed statistically by the test of Egger et al.¹⁵ The Peto method meta-analyses were performed with the Comprehensive Meta-Analysis Software version 2 (Biostat, Engle-wood, NJ). Statistical significance for the two-tailed *P* values was set, a priori, as <.05.

Role of the Funding Sources

The funding sources had no input into the study design, collection, analysis, or interpretation of the data, manuscript preparation, or in the decision to submit the manuscript for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Initially, 7 studies were identified from the total of 272 screened, but one was excluded because the outcome data could not be extracted for the 2 treatment groups (Figure 1).¹⁶ Of the 6 eligible studies^{17–22} included in the meta-analysis for HBV recurrence, 2 were prospective,^{18,21} and 4 were retrospective^{17,19,20,22} (Table 1). All studies were published in English and were conducted in the following countries: 1 each in Australia,²¹ Spain,²² and France,¹⁸ and 3 in the United States.^{17,19,20} In the 6 trials, 193 patients received HBIG and LAM, and 124 patients received HBIG monotherapy. HBV-related death could only be assessed in 3 studies (1 prospective¹⁸ and 2 retrospective^{17,20}). In these 3 trials, 115 patients received HBIG and LAM combination therapy, and 85 patients received HBIG monotherapy. Five studies uniformly reported that all-cause mortality was lower in the HBIG and LAM combination therapy groups

as compared with HBIG monotherapy, but only 3 studies provided quantitative data on all-cause mortality to conduct a meta-analysis (1 prospective²¹ and 2 retrospective^{19,20}).

Meta-analysis

All the studies showed benefit of HBIG and LAM combination therapy over HBIG alone (Figure 2). None of the studies reported any harmful effects of combination therapy. The cumulative rate of recurrence of HBV in the HBIG and LAM combination therapy versus HBIG alone was 4.1% versus 36.1%, respectively, and the HBV-related death and all-cause mortality rates were 0.8% versus 15.1% and 5.1% versus 22.2%, respectively. Thus, the numbers needed to treat to prevent one HBV recurrence, HBV-related death, and all-cause mortality would be 4, 7, and 6 patients, respectively. The summary ORs (95% CI) showing risk reduction with the combination of LAM and HBIG versus HBIG alone for HBV recurrence, HBV-related death, and all-cause mortality were 0.08 (95% CI, 0.03–0.21; $P < .001$), 0.08 (95% CI, 0.02–0.33; $P < .001$), and 0.21 (95% CI, 0.06–0.82; $P = .02$), respectively. The exact methods gave similar results.

Heterogeneity and Publication Bias

For the primary outcome analysis, the P value for the Q statistic was nominal ($P > .13$), indicating a lack of heterogeneity across studies. The exact P value for the Breslow-Day test for heterogeneity was .24. There was no obvious publication bias among the studies based on the funnel plot (data not shown) and the Egger regression method (intercept, -0.96 ; $P = .21$).

Discussion

The results of this meta-analysis indicated that the HBIG and LAM combination therapy is markedly better than HBIG alone in the post-liver transplantation setting for the prevention of HBV recurrence, HBV-related death, and all-cause mortality. The use of combination regimen as compared with HBIG alone reduced the odds of HBV recurrence, HBV-related death, and all-cause mortality by 12-, 12-, and 5-fold, respectively. These results have important clinical and public policy implications because HBIG has recently been approved for the treatment of patients infected with hepatitis B who are receiving liver transplants. Although the HBIG and LAM combination therapy is more expensive than monotherapy with either agent alone, in lieu of its much greater efficacy compared with HBIG alone, the use of this combination is preferred for the prevention of HBV recurrence and for the subsequent mortality in this setting. However, there are several unresolved issues that merit future studies including the duration, dose, and route of administration of HBIG.²³ In addition, further studies are needed to examine whether newer anti-HBV agents such as entecavir, telbivudine, adefovir, or tenofovir would be more efficacious as part of combination therapy with HBIG instead of LAM.^{4,24,25}

Limitations of our study include lack of availability of source and time to event data, small number of studies, limited sample sizes, absence of randomized controlled studies, and variable post-transplant immunosuppression protocols used in different transplant centers. None of the studies were randomized, and all used historical controls. Although often unclear, the studies did not have a fixed manner to follow patients and lacked strict a priori definition of outcomes. In 3 of the 6 studies included in this meta-analysis, the duration of follow-up was longer for the HBIG monotherapy group (Table 1.). Furthermore, most studies did not provide adequate information on patient adherence to treatment or procedures. In addition, there is a potential for variability in HBV DNA assays between studies. Although previous studies have reported that HBIG at lower doses is as effective as the high-dose HBIG and pretreatment HBV DNA levels increase the risk of HBV recurrence, these variables could not be independently analyzed because of lack of data in individual studies.¹⁰ Whether a shorter course of HBIG followed by

continuation of LAM or alternative agents might be adequate in this setting could not be examined because of insufficient data.^{26,27}

Despite its limitations, our meta-analysis showed that the HBIG and LAM combination therapy is much more effective than HBIG alone in reducing HBV recurrence and mortality in HBV-infected patients after liver transplantation. LAM also has been found to have an excellent safety record. However, further research is needed to determine the duration of HBIG after liver transplant and whether HBIG can be stopped or patients can be switched to lower doses of HBIG after a defined period of time after liver transplant. Also important are the roles of LAM resistance and the safety of other newer nucleoside analogues in this setting. This study provides a benchmark to assess potentially higher efficacy of newer anti-HBV agents and HBIG as compared with LAM and HBIG in the prevention of HBV recurrence and reduction of HBV-related death and all-cause mortality after liver transplantation.

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Abbreviations in this paper

CI	confidence interval
HBIG	hepatitis B immunoglobulin
LAM	lamivudine
OR	odds ratio

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Figure 1.

Selection of studies for meta-analysis regarding the effect of HBIG and LAM combination therapy vs HBIG monotherapy on HBV recurrence in patients receiving liver transplant.

Figure 2.

Meta-analysis regarding the effect of HBIG and LAM combination therapy vs HBIG monotherapy on HBV recurrence in patients receiving liver transplant.

Demographics of Liver Transplant Patients Receiving HBIG With and Without LAM in 6 Studies Considered Eligible for Meta-analysis

Table 1

Lead author (y)	McCaughan (1999)		Han (2000)		Anselmo (2002)		Honaker (2002)		Dumortier (2003)		Sousa ^d (2003)	
Country of origin	Australia		USA		USA		USA		France		Spain	
Study arm ^b	HBIG ^c	HBIG + LAM ^d	HBIG	HBIG + LAM	HBIG	HBIG + LAM	HBIG	HBIG + LAM	HBIG	HBIG + LAM	HBIG	HBIG + LAM
No. of patients	10	9	12	59	28	89	14	9	43	17	17	10
Age, median (y) (range)	50 (38–61)	50 (30–59)	44 (23–59)	50 (18–67)	49 (12–73)	48 (NR)	43 (NR)	48 (NR)	40 (NR)	50 (NR)	46 (NR)	46 (NR)
Gender (male/female)	9/1	8/1	8/4	47/12	136/20	7/2	11/3	7/2	35/8	15/2	21/6	21/6
HBV DNA (positive/negative) ^e	All positive		Positive and negative		23/89		10/4		4/5		All negative	
Immunosuppression at the time of transplant	Azathioprine, cyclosporine, prednisone		Cyclosporine, steroids, tacrolimus		Azathioprine, cyclosporine, prednisone, tacrolimus		Cyclosporine, prednisone, tacrolimus		Azathioprine, cyclosporine, mycophenolate, tacrolimus		NR	
Duration of follow-up, median mo (range)	7 (4–75)	15 (4–24)	15 (1–86)	15 (1–62)	29 (4–204)	48	72	48	98 (57–137)	30 (12–48)	71	30
HBV reactivation ^f	9	0	3	0	13	10	3	0	10	0	4	0
HBV-related deaths ^g	None		None		9	2	2	0	5	0	None	

NR, not reported.

^aDemographic data: age, gender, HBV DNA, and follow-up are combined among all study arms including no treatment, HBIG monotherapy, LAM monotherapy, and HBIG and LAM combination therapy groups.

^bAll patients had a pretransplant diagnosis of one of the following: cirrhosis, chronic HBV, or hepatocellular carcinoma.

^cAll patients received in both study arms HBIG IV 10,000 IU (anhepatic), then once daily for up to 7–9 days, then once every 4–8 weeks up to 1 year, except McCaughan, who gave HBIG IM 400 IU immediately postoperatively, then daily for 1 week, then weekly until time of discharge, and then monthly.

^dAll patients received LAM 150 mg/day, except McCaughan (patients assumed to have received 100–150 mg/day) and Sousa (patients received 100 mg/day).

^eHBV DNA positivity defined as any detectable level or according to study definition.

^fHBV recurrence was defined as the reappearance of HBsAg in the serum after transplant or according to study definition.

^gDeath or survival outcomes were based on either median or minimum follow-up for both study arms.