ORIGINAL ARTICLE

Recurrence of Hepatitis B Is Associated With Cumulative Corticosteroid Dose and Chemotherapy Against Hepatocellular Carcinoma Recurrence After Liver Transplantation

Nam-Joon Yi,[1] Kyung-Suk Suh,[1] Jai Young Cho,[1] Choon Hyuck Kwon,[2] Kwang-Woong Lee,[2] Jae Won Joh,[2] Suk-Koo Lee,[2] Soon Il Kim,[3] and Kuhn Uk Lee[1]

[1]Department of Surgery, Seoul National University College of Medicine; [2]Department of Surgery, Samsung Medical Center, Sungkyunkwan University, School of Medicine; and [3]Department of Surgery, Yonsei University College of Medicine, Seoul, Korea

The incidence of hepatitis B (HB) recurrence after a liver transplantation has been reduced by prophylaxis with hepatitis B immunoglobulin (HBIG) and lamivudine. However, the long-term incidence of recurrence is <10%, and the factors associated with HB recurrence are unclear. This study analyzed the factors associated with HB recurrence in 203 recipients who underwent liver transplantation for HB in 3 major centers in Korea over 4 years. Eighty-five patients (41.9%) had a hepatocellular carcinoma (HCC). Preoperative active virus replicators with the HBeAg(+) (46.8%) and/or hepatitis B virus DNA(+) (39.4%) were observed in 136 patients (67.0%). The HB prophylaxis consisted of either HBIG monotherapy (n = 95, HBIG group) or combination therapy with lamivudine (n = 108, combination group). HB recurrence was defined as the appearance of the HBsAg. The follow-up period was 28.3 ± 13.1 months (mean ± SD). HB recurred in 21 patients (10.3%) after transplantation. The time from transplantation to recurrence was 16.3 ± 9.4 months. Pre-LT DNA positivity was more prevalent in HBIG group (55.8%) than in the combination group (39.8%) ($P = 0.015$). However, the incidence of HB recurrence was similar in the HBIG (6.3%) and combination group (13.8%), as well as between the active replicators (12.5%) and nonreplicators (4.1%) ($P < 0.05$). There was a far higher incidence of HB recurrence in patients receiving corticosteroid pulse therapy (21.0% vs. 7.9%), patients who experienced HCC recurrence (31.3% vs. 8.6%), and patients receiving chemotherapy to prevent HCC recurrence (25.0% vs. 4.4%) ($P < 0.05$). The cumulative corticosteroid dose was higher in patients who experienced recurrence of HB ($P = 0.002$). Multivariable analysis confirmed the effect of the cumulative corticosteroid dose and chemotherapy to be risk factors. Liver transplantation for HB is safe, with low recurrence rates if adequate prophylaxis is used. However, the cumulative corticosteroid dose and the chemotherapy used for HCC were risk factors for HB recurrence, so careful monitoring for HB recurrence is needed in these patients. ***Liver Transpl 13:451-458, 2007.*** © **2007 AASLD.**

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The outcome of liver transplantation (LT) for hepatitis B virus (HBV)-related liver diseases was dismal before the advent of an effective means for preventing the virtually universal reinfection of the graft. Reinfection was followed by progressive destruction by recurrent hepatitis. This led to quick graft failure. HBV-related liver disease was once considered to be a contraindication for LT. However, over the last 15 years, there have been major advances in the management of transplant candidates with hepatitis B (HB). The long-term use of

Abbreviations: ACR, acute cellular rejection; anti-HBc, hepatitis B core antibody; HB, hepatitis B; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B s antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LFT, liver function test; LT, liver transplantation.

Address reprint requests to Kyung-Suk Suh MD, PhD, Department of Surgery, Seoul National University College of Medicine, 28 Yongon-Dong, Chongno-Gu, Seoul, Korea 110-744. Telephone: 82-2-2072-3789; FAX: 82-2-766-3975; E-mail: kssuh@plaza.snu.ac.kr

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TABLE 1. Clinical Features of 203 Hepatitis B Virus–Related Liver Disease Patients at Time of Transplantation According to Posttransplantation Prophylactic Regimen

Characteristic	Total (n = 203)	HBIG group (n = 95)	Combination group (n = 108)	*P* value
Gender (male: female)	162:41	80:15	82:26	0.163
Mean age (yr) (mean ± SD)	46.9 ± 8.0	46.6 ± 7.5	47.3 ± 8.4	0.690
Active replicator*	136 (67.0%)	63 (66.3%)	73 (67.6%)	1.000
HBeAg positivity	95 (46.8%)	39 (41.1%)	56 (51.9%)	0.253
HBV DNA				
Positivity	80 (39.4%)	53 (55.8%)	43 (390.8%)	0.015
Titer (pg/dL) (mean ± SD)	215.5 ± 674.6	348.1 ± 898.2	610.3 ± 1,080.8	0.007
Donor anti-HBc positivity	92 (45.3%)	42 (44.2%)	50 (47.6%)	0.424
HCV coinfection	3 (1.5%)	2 (2.1%)	1 (0.9%)	0.600
HCC	85 (41.9%)	46 (48.4%)	39 (36.1%)	0.088
UNOS status				0.532
1	2 (1.0%)	0	2 (10.9%)	
2A	49 (24.1%)	24 (25.3%)	25 (230.0%)	
2B	114 (56.2%)	60 (63.1%)	74 (680.5%)	
Pre-LT lamivudine therapy	55 (27.1%)	29 (31.2%)	26 (24.3%)	0.071
Duration (months) (mean ± SD)	7.6 ± 7.8	9.7 ± 7.9	50.5 ± 70.4	0.189

Abbreviations: HBIG, hepatitis B immunoglobulin; HBeAg, HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC hepatocellular carcinoma; UNOS, United Network for Organ Sharing; LT, liver transplantation.
*HBeAg and/or HBV DNA positive recipients.

hepatitis B immunoglobulin (HBIG) therapy and the introduction of new antiviral agents, such as lamivudine, against HBV infections have been major breakthroughs.[1,2] Today, the results of LT for HBV-related liver disease are similar to that of patients receiving transplants for other indications. Nevertheless, 10% of LT patients with underlying HB experience a recurrence.[3-5] The factors associated with HB recurrence are unclear.

This study examined 203 patients who underwent LT for HBV-related liver disease in 3 major centers in Korea, with the aim of evaluating the risk factors associated with HB recurrence and the safety of the HB prophylactic protocol after LT in the era of HBIG and lamivudine.

METHODS

Between January 1999 and December 2002, a total of 203 adult patients (age 18 years or older) who underwent LT for HBV-related liver disease and were followed up for at least 6 months were enrolled onto this study. The mean interval between registration to the Korean Network for Organ Sharing and the transplantation was 5.4 ± 7.9 months (mean ± SD, range, 0-64.4 months).

Table 1 summarizes the patients' data at the time of transplantation. There were 151 cases of living donor LT and 56 cases of deceased donor LT, including 4 cases of retransplantation. A hepatitis C virus coinfection was found in 3 cases (1.5%). Eighty-five patients (41.9%) were associated with a hepatocellular carcinoma (HCC). A replicative HBV infection was defined as the presence of the hepatitis e antigen (HBeAg) and/or HBV DNA in serum. The HBV DNA was tested by means of a nonamplified hybrid capture assay with a branched-chain DNA assay (Greencross, Korea). The detection threshold for the DNA was 105 copies/mL. One hundred thirty-six patients (67.0%) were pre-LT active replicators at the time of the transplantation. HBeAg positivity and HBV DNA positivity was noted in 95 (46.8%) and 80 patients (39.4%), respectively. There were 92 patients (45.3%) whose donor tested positive to serum antibody against the hepatitis B core antigen (anti-HBc). There were 2 cases (1.0%) of fulminant hepatitis B.

Pretransplantation lamivudine therapy for active replicators was not a routine protocol. Pretransplantation lamivudine therapy was initiated in 55 patients (27.1%). Forty (30.3%) of 136 pre-LT active replicators underwent pretransplantation lamivudine therapy. Overall, the mean duration of pretransplantation lamivudine therapy was 2.1 ± 5.3 months (range, 0.5-27.5 months). There were 2 patients with breakthrough infection, but no patients underwent pretransplantation adefovir therapy.

The prophylactic infusion of human HBV-specific hepatitis B immunoglobulin (HBIG, anti–hepatitis B immunoglobulin, Greencross, Korea) was administered intravenously to all patients after LT (Fig. 1). HBIG was initiated at the time of transplantation and was continued indefinitely. HBIG was administered at 10,000-20,000 IU during the anhepatic phase and 10,000 IU daily for 7 days, followed by 10,000 IU weekly for the first month. Thereafter, the HBIG load was measured in order to maintain the anti-HBs titers at >350 IU/L for combination therapy with lamivudine, or the HBIG dose was fixed at 10,000 IU for HBIG monotherapy every month for the first year. After then, the HBIG dose

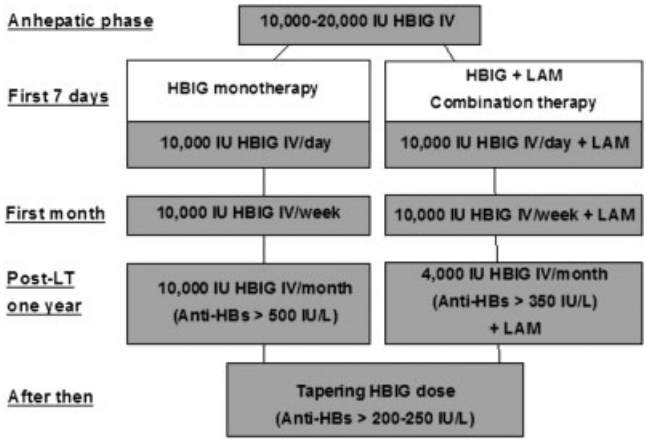

Figure 1. Hepatitis B prophylaxis using hepatitis B immunoglobulin (HBIG) and lamivudine (LAM) after liver transplantation.

was reduced every 4-8 weeks in order to maintain the anti-HBs titers at <200 to 250 IU/L, and lamivudine was discontinued in combination therapy.

Ninety-five patients (46.8%) did not receive lamivudine and were treated with HBIG only after the liver transplantation (HBIG monotherapy, HBIG group). One hundred eight patients (53.2%) were treated with lamivudine combined with HBIG after the liver transplantation (HBIG and lamivudine combination therapy, combination group) at a daily dose of 25-100 mg according to renal function. The prophylactic regimen was determined according to guideline of the each center; Samsung Medical Center used HBIG monotherapy, and the other centers used combination therapy. Adefovir was not provided as a primary treatment after transplantation in this study. Both the HBIG and combination groups were comparable with regard to the pre-LT clinical features (Table 1). However, the HBV DNA positivity and titer were much different. HBV DNA positivity was more frequent in the HBIG group (55.8%) than in the combination group (39.8%) ($P = 0.015$). HBV DNA titer was higher in the HBIG group (305.5 ± 848.7 pg/dL) than in the combination group (35.6 ± 88.9 pg/dL) ($P = 0.007$).

A calcineurin inhibitor plus a corticosteroid-based protocol was used as the immunosuppressive therapy. Corticosteroids were gradually discontinued 12 months after LT. Mycophenolate mofetil and basiliximab were used as rescue therapy for any renal insufficiency or as a primary therapy in selected patients.

Acute cellular rejection (ACR) was defined by liver biopsy.[6] In the case of ACR, a 500-mg intravenous bolus of methylprednisolone was administered for 1-3 days, followed by a rapidly tapered regimen of intravenous corticosteroid within 5-7 days. Oral corticosteroid was tapered within 3-6 months after treatment for ACR. There was no single prescribed corticosteroid therapy for life.

The recurrence of the HBV was defined as the appearance of the hepatitis B s antigen (HBsAg) in the serum after LT.[5,7] The post-LT anti-HBs titer and clinical data were collected every month after surgery. HBsAg and any breakthrough infection were routinely monitored in any patient with an abnormal liver function test (LFT) and in cases of a sudden decrease in the anti-HBs titer under HBIG therapy, as well as 1 year after the transplantation in both the HBIG and combination groups.

Any HB recurrence after LT was initially treated with lamivudine in the HBIG group and in combination group where the lamivudine had been discontinued. In the case of lamivudine resistance, the lamivudine treatment was switched to or combined with adefovir.

After LT, the patients were followed up for a mean time of 28.3 ± 13.1 months (range, 6.1-60.3 months). The data were analyzed from the time of enrollment (between January 1, 1999, and December 31, 2001) until the study closure date (January 1, 2004) or death.

Statistical Analysis

Statistical analyses were performed by SPSS 10.0 statistical software (SPSS, Chicago, IL). The categorical variables were compared by Fisher's exact test. The continuous variables were compared by nonparametric Mann-Whitney *U* test. The variables were compared by the proportional hazard regression analysis to determine the independent predictive factors for HB recurrence after LT. The variables reaching statistical significance by univariate analysis were then included for multivariate analysis. $P < 0.05$ was considered to be statistically significant. Continuous normally distributed variables are represented as means ± SD.

RESULTS

The overall 1- and 3-year survival rates were 94.6% and 90.1%, respectively. Overall, HB relapsed in 10.3% of these recipients (21 of 203) with a 3-year actuarial risk of 13.2% (7 of 53). The mean interval to recurrence after the transplantation was 16.3 ± 9.4 months (range, 2-40 months). A sudden drop in the anti-HBs titer indicated the recurrence of HB, irrespective of the LFT. Two patients showed an abnormal LFT without any changes in the anti-HBs titer.

There was no statistically significant differences in the post-LT HB recurrence according to the recipients' gender ($P = 0.150$), age ($P = 0.555$), United Network for Organ Sharing status ($P = 0.533$), graft type ($P = 0.214$), pre-LT active replicator ($P = 0.223$), pre-LT HBeAg positivity ($P = 0.768$), pre-LT HBV DNA positivity ($P = 0.115$), pre-LT HBV DNA titer ($P = 0.934$), donor anti-HBc positivity ($P = 0.694$), pre-LT HCC ($P = 0.238$), pre-LT lamivudine therapy ($P = 0.976$), the duration of pre-LT lamivudine therapy ($P = 0.109$), types of post-LT prophylaxis ($P = 0.292$), and the duration of corticosteroid therapy ($P = 0.083$). Corticosteroid pulse therapy ($P = 0.000$), the cumulative dose of corticosteroid ($P = 0.002$), the recurrence of the HCC ($P = 0.000$), and systemic chemotherapy against HCC recurrence ($P = 0.0001$) were associated with post-LT HB recurrence (Table 2).

Thirty-eight (18.7%) of 203 patients experienced ACR

TABLE 2. Univariate analysis for the risk factors associated with the recurrence of hepatitis B after liver transplantation

Variable	Post-LT HB recurrence (%)		*P* value
	Yes	No	
Gender			0.150
Male	19 (11.7)	143 (88.3)	
Female	2 (4.9)	39 (95.1)	
Age; years (mean ± SD)	47.0 ± 7.8	46.9 ± 8.0	0.555
UNOS status			0.533
1, 2A	4 (7.8)	47 (92.2)	
2B, 3	17 (11.2)	135 (88.8)	
Graft type			0.214
Partial	15 (10.0)	135 (90.0)	
Whole	6 (11.3)	47 (88.7)	
Pre-LT active replicator*			0.223
Yes	17 (12.5)	119 (87.5)	
No	2 (4.1)	49 (95.9)	
Pre-LT HBeAg positivity			0.768
Yes	12 (12.6)	83 (87.4)	
No	9 (8.9)	93 (91.1)	
Pre-LT HBV DNA positivity			0.115
Yes	12 (13.2)	79 (86.8)	
No	5 (5.9)	80 (94.1)	
Pre-LT HBV DNA titer; pg/mL (mean ± SD)	161.3 ± 260.8	103.0 ± 503.1	0.934
Donor anti-HBc positivity			0.694
Yes	12 (13.0)	80 (87.0)	
No	6 (8.8)	62 (91.2)	
HCC			0.238
Yes	11 (12.9)	74 (87.1)	
No	10 (8.5)	108 (91.5)	
Pre-LT lamivudine therapy			0.976
Yes	5 (9.1)	50 (90.9)	
No	15 (10.7)	125 (89.3)	
Duration of pre-LT lamivudine therapy; months (mean ± SD)	1.27 ± 0.46	1.36 ± 0.53	0.109
Post-LT combination therapy			0.292
Yes	15 (13.8)	93 (86.2)	
No	6 (6.3)	89 (93.7)	
Corticosteroid pulse therapy			0
Yes	8 (21.1)	30 (78.9)	
No	13 (7.8)	152 (92.2)	
Duration of corticosteroid therapy; months (mean ± SD)	14.1 ± 15.4	13.0 ± 11.4	0.083
Cumulative dose of corticosteroid; mg (mean ± SD)	3,824.6 ± 2,021.3	2,847.9 ± 1,143.4	0.002
HCC recurrence			0.000
Yes	5 (31.3)	11 (68.8)	
No	16 (8.6)	171 (91.4)	
Systemic chemotherapy against HCC recurrence			0.000
Yes	5 (38.5)	8 (61.5)	
No	16 (8.4)	174 (91.6)	

Abbreviations: LT, liver transplantation; HB, hepatitis B; HBV, hepatitis B virus; UNOS, United Network for Organ Sharing; HCC, hepatocellular carcinoma.
*HBeAg and/or HBV DNA positive recipients.

and underwent corticosteroid pulse therapy at 4.0 ± 4.7 months (range, 8 days to 16 months) after LT. No patient underwent antibody therapy because ACR was well controlled with corticosteroid therapy, except in one patient, who underwent retransplantation. Eight (21.1%) of 38 patients who underwent corticosteroid pulse therapy experienced HB recurrence, and 13 (7.8%) of 165 patients did not experience HB recurrence ($P = 0.000$). The median time to HB recurrence was 15.7 months (range, 1.5-24.7 months) after corticosteroid pulse therapy.

TABLE 3. Comparison of Risk Factors Associated With Recurrence of Hepatitis B After Liver Transplantation According to

Variable	HBIG group (n = 95)	Combination group (n = 108)	*P*-value
Corticosteroid pulse therapy	22 (23.2%)	16 (14.8%)	0.390
Duration of corticosteroid therapy; month (mean ± SD)	16.1 ± 13.7	10.2 ± 8.8	0.038
Cumulative dose of corticosteroid; mg (mean ± SD)	3,195.3 ± 1,473.3	2,740.1 ± 1,064.7	0.003
HCC recurrence	6 (6.3%)	10 (9.3%)	0.156
Systemic chemotherapy against HCC recurrence	5 (5.3%)	8 (7.4%)	0.579

Abbreviations: HBIG, hepatitis B immunoglobulin; HCC, hepatocellular carcinoma.

The mean duration of corticosteroid therapy was 13.1 ± 11.8 months, and cumulative corticosteroid dose was 2,942.1 ± 1,278.1 mg. There were no differences in the duration of corticosteroid therapy between the patients with HB recurrence (14.1 ± 15.4 months) and without recurrence (13.0 ± 11.4 months) (P = 0.083). However, the mean cumulative corticosteroid dose was higher in the patients with HB recurrence (3,824.6 ± 2,021.3 mg) than in those without recurrence (2,847.9 ± 1,143.4 mg) (P = 0.002).

Pretransplantation HCC itself was not associated with posttransplantation HB recurrence (P = 0.238). HCC recurrence was detected in 16 (7.9%) of 203 patients at 6.9 ± 9.1 months (range, 1.8-38.8 months). HCC recurrence had a marked effect on HB recurrence. HB recurred in 5 (31.3%) of 16 patients in whom HCC had recurred and in 16 (8.6%) of 171 patients in whom HCC did not (P = 0).

Treatment against HCC recurrence was begun at 7.1 ± 9.0 months (range, 2.0-39.7 months) after transplantation. Of the 16 patients with HCC recurrence, 13 patients (81.3%) received 5-fluorouracil–based systemic chemotherapy, 7 patients (43.8%) received radiation therapy, 6 patients (37.5%) received transhepatic arterial chemoembolization, and 5 patients (31.3%) underwent surgery. Ten of 16 patients underwent multimodality combination therapy. Systemic chemotherapy had a marked effect on HB recurrence. HB recurred in 5 (38.5%) of 13 posttransplantation systemic HCC treatment and in 15 (7.9%) of the other 190 patients (P = 0.000). However, no one experienced HB recurrence after locoregional treatment modality only, such as surgery, transarterial chemoembolization, or radiation therapy. The median time interval between systemic chemotherapy and HB recurrence was 5.2 months (range, 3.5-9.6 months).

Multivariate analysis revealed the cumulative dose of corticosteroid (P = 0.000, hazard ratio 19.596; 95% CI, 3.903-98.382) and systemic therapy against HCC recurrence (P = 0.001, hazard ratio 12.775; 95% CI, 2.900-56.269) to be statistically significantly associated with HB recurrence after liver transplantation, which confirms its independent predictive value in this setting.

The rate of HB recurrence between the HBIG group (6.3%) and combination group (13.8%) was similar (P = 0.292). Table 3 shows the risk factors for HB recurrence in both groups. There were no differences in corticosteroid pulse therapy (P = 0.390), HCC recurrence (P = 0.156), and systemic chemotherapy (P = 0.579) between the 2 groups. However, the duration of corticosteroid therapy (P = 0.038) and the cumulative corticosteroid dose (P = 0.003) were higher in the HBIG group than in the combination group, which was probably the result of differences in the corticosteroid tapering protocol used at each center.

In the 21 patients who experienced HB recurrence, lamivudine was administered to 6 patients, who were treated with HBIG monotherapy, and in 12 patients, who were treated with combination therapy, although the lamivudine had been discontinued. The other 3 patients were given combination therapy with no additional treatment. Two of these 3 patients had HB recurrence at 8 months and at 9 months after LT while receiving chemotherapy for systemic metastasis of the HCC, respectively. These patients died of metastasis 15 months and 13 months after transplantation, respectively. The third patient developed sepsis associated with biliary leakage 2 months after LT and experienced HB recurrence 7 months after LT. This patient died of multiorgan failure associated with biliary sepsis 10 months after transplantation.

None of the patients who experienced HB recurrence required adefovir as first-line therapy. Two of the patients who experienced HB recurrence were switched to adefovir therapy because of the presence of lamivudine-resistant mutants 12 and 14 months after lamivudine therapy, respectively.

The outcome of HB recurrence varied. Two (9.5%) of 21 HB recurrences experienced hepatic failure; one patient died, and the other underwent retransplantation but died of graft failure from an unknown origin. Four (19.5%) of these 21 patients showed an abnormal LFT; 2 of these 4 patients were switched to adefovir because of the presence of lamivudine-resistant mutants. The other patients (71.4%) responded well to lamivudine therapy and had a normal LFT.

DISCUSSION

The ideal regimen in the era of HBIG and lamivudine has not been identified until now.[8,9] The mechanism by

which HBIG prevents graft reinfection is unclear. HBIG may decrease the horizontal spread of an HBV infection within the liver by neutralizing the circulating virus particles and inducing the lysis of infected hepatocytes through a pathway such as antibody-dependent cellular cytotoxicity. The reduction of the circulating virions by HBIG may decrease the viral substrate available to lamivudine and decrease the emergence of drug-resistant mutants. On the other hand, the decrease in the virus load induced by lamivudine may prevent the saturation of the HBIG binding sites and reduce the immune pressure leading to the emergence of surface gene mutations. Therefore, the combined HBIG and lamivudine therapy might offer synergistic protection against graft reinfection, and the combination appears to be more effective than single-agent prophylaxis.[10] A guideline of HBV prophylaxis in an LT setting based on a European and an American perspective was provided. This involves the use of lamivudine or adefovir before LT, followed by combination therapy. This protocol provides improved control of virus replication before LT and complimentary forms of prophylaxis after LT to minimize the risk of reinfection. With this combination approach, the HB recurrence rate at 1-2 years after LT has been reduced to <10%.[8] In this study, the overall HB recurrence rate was 10.3%, which was comparable to other studies,[3-5,7-9] and there was no difference in the rates of HB recurrence between the HBIG group and combination group.

In this study, lamivudine was withdrawn at the end of the first postoperative year in the combination therapy. Prolonged lamivudine therapy in the posttransplantation setting can lead to the development of lamivudine-resistant mutants and may need high cost.[11] In addition, there is no prospective randomized study that has assessed whether post-LT long-term lamivudine therapy (1 year vs. < 1 year) with HBIG reduces HB recurrence. HBsAg, HBeAg, and HBV DNA were routinely checked 1 year after transplantation, and then lamivudine was stopped in the patients with negative serologic test with well-maintained LFT and anti-HBs titers in the combination group. Two (1.0%) of 203 patients showed positive HBV DNA 1 year later. They had negative 1-year HBsAg and HBeAg, and a good LFT, and anti-HBs titer was well maintained. We did not prescribe additional therapy because the significance of serum HBV DNA positivity in the absence of circulating HBsAg is uncertain.[12] Liver biopsy was carried out at 16 and 36 months after transplantation in one patient and at 38 months in the other. There were no lobular activities or portal fibrosis. The patients were followed up for 76 and 64 months and had no clinically relevant problems.

Until now, the factors associated with a lower incidence of HB recurrence were reported to be a negative the HBeAg and serum HBV DNA before LT, a hepatitis D virus superinfection, and fulminant hepatitis B.[1,2-4,7] Lamivudine resistance and a high HBV DNA load at the time of LT is associated with an increased risk of HB recurrence after receiving a liver transplant.[5] Therefore, pretransplantation lamivudine therapy is used to suppress HBV replication by achieving a loss of HBV DNA in 60-100% after 2-3 months of therapy.[13-15] However, pretransplantation lamivudine therapy has several disadvantages. Long-term lamivudine therapy is expensive, and its use results in the development of lamivudine-resistant mutations, which are one of the major risk factors of posttransplantation HB recurrence. In addition, there has been no prospective randomized study to prove the efficacy of pretransplantation lamivudine therapy on posttransplantation HB recurrence.[16] Pretransplantation lamivudine therapy was not a routine protocol in this study.

We did not clarify the role of pretransplantation active replicators on the posttransplantation HB recurrence because this study was a retrospective review and HBV DNA was monitored by an assay with detection limit of 5 log. However, the results of this study also suggested a role of the pre-LT virus load in post-LT HB recurrence. Seven of the 8 patients in this study who had experienced HB recurrence after corticosteroid pulse therapy had pre-LT active replicators. None of the pre-LT nonreplicators who underwent corticosteroid pulse therapy experienced HB recurrence. It appeared that pre-LT active virus replication had an effect on HB recurrence in patients with massive immunosuppression.

In addition, it is well known the serum anti-HBc positivity in donors is a marker for the risk of HBV transmission and reactivation after LT in HBsAg-negative naive patients.[17-20] In Korea, which has a persistent organ donor scarcity, an anti-HBc–positive donor liver cannot be avoided,[19-23] and it had no effect on the posttransplantation HB recurrence when an appropriate prophylactic regimen was in place.

This study shows that HB recurrence after LT was related to corticosteroid pulse therapy and cumulative corticosteroid dose. HB recurrence was detected in 8 (21.1%) of 38 ACR cases. The interaction between corticosteroid pulse therapy and HB recurrence is unclear but can be explained as follows. The HBV has a corticosteroid receptor that promotes virus replication. Moreover, immunosuppressive therapy itself reactivates HBV replication. The increased totality of immunosuppression, particularly because corticosteroid pulse therapy in the early phase after LT can participate in HB recurrence but a long duration of low-dose corticosteroid therapy itself cannot. The mechanism for how early corticosteroid pulse therapy affects the late onset of HB recurrence is unclear but can be explained as follows: Massive immunosuppression with corticosteroid pulse therapy allows virus replication with a consequent increase in hepatocyte infection. However, in the early post-LT period, high-dose HBIG reduces the serum HBsAg to less than the detection level. At the same time, maintenance immunosuppressive therapy may delay or mask the destruction of the infected hepatocytes. The withdrawal or tapering of these HBV prophylactic drugs results in HBV expression in the serum to reach detection level. Moreover, the partial restoration of immunocompetence leads to the rapid destruction of the infected hepatocytes.

Because an increased cumulative dose of corticosteroid as a consequence of corticosteroid pulse therapy

can be a risk factor for HB recurrence after LT, care should be taken when deciding the appropriate treatment for ACR. The histopathological diagnosis of ACR may not automatically signal that a treatment is indicated, particularly if it is low grade. Because ACR is less frequent in living donor LT,[24] it is more often affected by more than one condition, such as preservation-related problems or vascular or biliary tree problems, which are widely considered to be completely reversible phenomena.[6]

Multivariate analysis showed that systemic chemotherapy against the recurrence of HCC also had an effect on HB recurrence, even though all patients with HCC recurrence continued to receive prophylactic therapy against HBV and their prechemotherapy LFT and anti-HBs titer were well maintained. A recurrence of HCC was noted in 16 patients at the following sites: liver (n = 5), bone (n = 4), lung (n = 3), peritoneum (n = 2), lymph nodes (n = 2), spleen (n = 1), and adrenal glands (n = 1). Thirteen of these 16 recipients died from progression of HCC. HB recurred in 5 (31.3%) of 16 recipients in whom HCC recurred. These 5 patients experienced HB recurrence after systemic chemotherapy against HCC recurrence. It is well documented that cytotoxic treatment in patients carrying HBV enhances the risk of severe hepatic damage[25-28] as a result of the breakthrough of the host immune barrier by means of cytotoxic chemotherapy. However, the validity of this correlation has not been established in clinical trials with a LT setting for HB, particularly under adequate HB prophylaxis. The median duration between systemic chemotherapy and HB recurrence (5.2 months) was shorter than that between corticosteroid pulse therapy and HB recurrence (15.7 months). It is possible that HCC recurrence itself is a product of any breakthrough of the host immunity, and active cell proliferation in a malignant transformation can induce active replication of the HBV in the liver.[29] This complexity of the mechanism of cytotoxic systemic chemotherapy may affect HB recurrence. We had been unaware that systemic chemotherapy could be a risk factor for the recurrence of HB in patients receiving routine antiviral prophylaxis after LT. For this reason, the prophylactic protocol against the HBV was not changed in those patients. However, we now recommend more intensive monitoring and antiviral prophylaxis in those patients.

The natural course of a recurrent HB infection under immunosuppression after liver transplantation is much more aggressive than in nonimmunosuppressed patients. However, the treatment for recurrent HB in liver transplant recipients is now much less of a clinical problem than before.[8] The optimal therapy for those HB-infected liver transplant recipients depends on the treatments previously received. A rapid reduction in immunosuppressive therapy is a common practice, and effective antiviral therapy is essential for preventing disease progression.[8]

In conclusion, despite the limitations of this retrospective analysis, this study showed that LT for HBV-related liver disease was safe and associated with low recurrence rates if adequate prophylaxis was provided. However, the cumulative corticosteroid dose and systemic chemotherapy against the recurrence of HCC had an effect on HB recurrence under an adequate prophylactic regimen. Therefore, physicians must be aware of this problem, monitor for HB recurrence, and consider additional powerful prophylaxis against HBV in these patients.

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