

Outcome of Liver Transplantation for Hepatitis B: Report of a Single Center's Experience

Chi-Jen Chu,* Robert J. Fontana,* Charles Moore,† Douglas R. Armstrong,† Jeffrey D. Punch,† Grace L. Su,* John C. Magee,† Robert M. Merion,† and Anna S.F. Lok*

Results of liver transplantation (LT) for hepatitis B have improved significantly with the use of hepatitis B immune globulin (HBIG) and/or lamivudine. The aim of this study is to review the long-term outcome of patients who underwent LT for hepatitis B. Records of 41 patients who underwent LT for hepatitis B and survived 3 months or longer post-LT were reviewed. Twenty patients were administered no immunoprophylaxis or short-term intramuscular HBIG, whereas 21 patients were administered high-dose intravenous (IV) HBIG. Median post-LT follow-up in these 2 groups was 76 months (range, 4 to 155 months) and 25 months (range, 4 to 68 months), respectively. Hepatitis B recurred in 15 (75%) and 4 patients (19%) who underwent LT in the pre-HBIG and post-HBIG eras, respectively. Cumulative rates of recurrent hepatitis B at 1 and 3 years post-LT in these 2 groups were 66% and 77% and 20% and 20%, respectively ($P < .001$). Recurrent hepatitis B in the post-HBIG era correlated with antibody to hepatitis B surface antigen titer less than 100 IU/L. Nine patients with recurrent hepatitis B were administered lamivudine for 13 to 49 months (median, 28 months); 6 patients continued to have stable or improved liver disease, whereas 3 patients developed virological breakthrough with slow deterioration of liver disease. Long-term IV HBIG is effective in preventing recurrent hepatitis B. The risk for recurrent hepatitis B is negligible after the first year post-LT. Among patients with no virological breakthrough, lamivudine can stabilize or improve liver disease for up to 4 years in patients with recurrent hepatitis B post-LT. (*Liver Transpl* 2001;7:724-731.)

Early results of liver transplantation (LT) for hepatitis B were poor, with a recurrent hepatitis B rate of 80% and 2-year mortality rate of 50%.¹⁻³ Long-term (>6 months) immunoprophylaxis with high-dose hepatitis B immune globulin (HBIG) has been effective in reducing the rates of recurrent hepatitis B, as well as

graft and patient mortality, after LT.⁴⁻⁷ Nevertheless, hepatitis B still recurs in some patients administered long-term HBIG therapy. Recurrence may be secondary to a high viral load pre-LT or immune escape mutations in the hepatitis B virus (HBV) S gene.^{8,9} Overall recurrence rates with HBIG monotherapy vary from 15% to 50%, but may be as high as 80% in patients who are hepatitis B e antigen (HBeAg) or HBV DNA positive before LT.^{4,10-15} Pharmacokinetic studies showed significant variability in antibody to hepatitis B surface antigen (anti-HBs) titers post-LT, particularly during the first 3 months.¹⁶ Until now, the efficacy of HBIG beyond the first 2 to 3 years post-LT has not been reported.

In the last few years, lamivudine has been shown to be effective in decreasing recurrent hepatitis B post-LT.^{17,18} However, the long-term efficacy of lamivudine monotherapy may be limited by the selection of drug-resistant mutants.¹⁹ Recent studies showed that the combination of HBIG and lamivudine may be more effective and may reduce recurrent hepatitis B to less than 5%; however, the number of patients involved in these studies is small, and the duration of post-LT follow-up is limited.²⁰⁻²³

Lamivudine also has been shown to be effective in the treatment of patients with recurrent hepatitis B post-LT.²⁴ However, breakthrough infection caused by lamivudine-resistant mutants developed in 27% of patients after 1 year of treatment. Thus, the long-term benefits of lamivudine treatment in patients with recurrent hepatitis B post-LT remain to be determined.

The primary aim of this study is to review the long-term outcome of patients who underwent LT for hepatitis B. Secondary aims are to determine (1) the efficacy of indefinite high-dose HBIG in the prevention of recurrent hepatitis B, and (2) long-term safety and efficacy of lamivudine in the treatment of recurrent hepatitis B.

Patients and Methods

Patients

Between January 1984 and May 2000, a total of 930 patients underwent LT at the University of Michigan Medical Center

From the *Department of Medicine, Division of Gastroenterology, and †Department of Surgery, Division of Transplant Surgery, University of Michigan Medical Center, Ann Arbor, MI.

Address reprint requests to Anna S.F. Lok, MD, Division of Gastroenterology, University of Michigan Medical Center, 3912 Taubman Center, Box 0362, Ann Arbor, MI 48109. Telephone: 734-615-4628; FAX: 734-936-7392; E-mail: aslok@umich.edu

Copyright © 2001 by the American Association for the Study of Liver Diseases

1527-6465/01/0708-0005\$35.00/0

doi:10.1053/jlts.2001.26062

Table 1. Characteristics of Patients at Transplant Listing

	Pre-HBIG Era (n = 20)	Post-HBIG Era (n = 21)	P
Age (yr)	38 ± 3	49 ± 2	<.01
Men/women	17/3	19/2	NS
White/black/Asian	18/2/0	20/1/0	NS
Cirrhosis/FHF/HCC	17/3/0	18/2/1	NS
1 st /re-LT	19/1	17/4	NS
HCV coinfection	1/3	3/17	NS
HDV coinfection	0/12	2/10	NS
HBeAg	7/13	14/19	NS
HBV DNA	NA	13/17	

Abbreviations: NS, not significant; FHF, fulminant hepatic failure; HCC, hepatocellular carcinoma; NA, not available.

(Ann Arbor, MI). Fifty-nine patients (6.3%) underwent LT for HBV-related acute or chronic liver failure. All patients had detectable hepatitis B surface antigen (HBsAg) in serum at the time of LT. Medical records of 41 patients who survived more than 3 months post-LT were reviewed to assess hepatitis B recurrence and outcome (Table 1). For each patient, baseline demographic data, indications for LT, and results of sequential liver biochemistry tests, hepatitis B serological tests, and HBV DNA tests, as well as the use of antiviral therapy pre-LT and prophylactic immune/antiviral therapies post-LT, were recorded.

Outcome

Primary outcomes of this study are patient survival and rate of recurrent hepatitis B post-LT. Recurrent hepatitis B is defined as the detection of HBsAg more than 1 month post-LT. Breakthrough HBV infection during lamivudine therapy is defined as the persistent reappearance of HBV DNA in serum after its initial disappearance on at least 2 occasions, determined by non-polymerase chain reaction (PCR)-based assays.

Prophylactic Therapy

Patients were divided into 2 groups based on the use of immunoprophylaxis post-LT. During the pre-HBIG era (before January 1994), 20 patients were administered no or only short-term (<6 months) intramuscular HBIG (Abbott Laboratories, Abbott Park, IL). In the post-HBIG era (after January 1994), 21 patients were administered 10,000 IU of intravenous (IV) HBIG during the anhepatic phase, daily for the next 6 days, and monthly thereafter (Table 1). HBIG protocols were approved by the University of Michigan Institution Review Board. Four patients in the post-HBIG era were also administered lamivudine (100 mg/d) before LT (median, 9.5 months; range, 1 to 17 months). These 4 patients were administered the same dose of HBIG as listed. Three patients were HBeAg positive and had detectable HBV DNA before lamivudine treatment. All 3 patients had unde-

etectable HBV DNA and cleared HBeAg before LT. No patient developed lamivudine resistance before LT.

Monitoring Post-LT

During the pre-HBIG era, patients were followed up monthly during the first year post-LT and every 3 to 6 months thereafter. During the post-HBIG era, patients were administered monthly HBIG infusions and follow-up care at the Transplant Ambulatory Care Unit. Hepatitis B serological assays were performed every 3 to 6 months during the pre-HBIG era. HBsAg and trough anti-HBs titers were checked before each infusion, and serum HBV DNA was tested every 4 months in the post-HBIG era.

Hepatitis serological tests (HBsAg, HBeAg, anti-HBs, antibody to HBeAg, antibody to hepatitis C virus, and antibody to hepatitis D virus [HDV]) were performed using commercially available enzyme-linked immunoassays (Abbott Laboratories). Serum HBV DNA was determined by non-PCR-based assays, which included liquid hybridization (Abbott) and branched DNA assays (Bayer Corp, Norwood, MA). Serum anti-HBs titer was measured using an enzyme-linked assay (AUSAB; Abbott). Lamivudine-resistant HBV P gene mutations were examined by PCR and direct sequencing.²⁵

Management of Patients With Recurrent Hepatitis B Post-LT

Before the availability of lamivudine, patients with recurrent hepatitis B did not undergo antiviral therapy. Re-LT was performed in selected patients with recurrent liver failure. After lamivudine became available in 1996, 9 patients with recurrent hepatitis B were treated with lamivudine (100 mg/d). Of these, 7 patients underwent LT in the pre-HBIG, and 2 patients, in the post-HBIG era. The latter 2 patients had not been administered lamivudine previously.

Statistical Analyses

Data were entered into an Excel (Microsoft Corp, Redmond, WA) database and analyzed using SPSS version 9.0 software package (SPSS Inc, Chicago, IL). Statistical analyses were performed using Chi-squared and Fisher's exact tests for categorical variables. Paired and unpaired Student's *t*-tests were used for continuous variables. Time to recurrent hepatitis B was estimated using the Kaplan-Meier method and compared using the log-rank test. Results are considered statistically significant at $P < .05$.

Results

Baseline characteristics of the patients are listed in Table 1. Sex, ethnicity, indications for LT, frequency of HDV coinfection, HBeAg status at listing, and liver biochemistry test results at LT were similar between the 2 groups. However, patients who underwent LT in the pre-HBIG era were significantly younger ($P < .01$).

Most patients who underwent LT in the post-HBIG

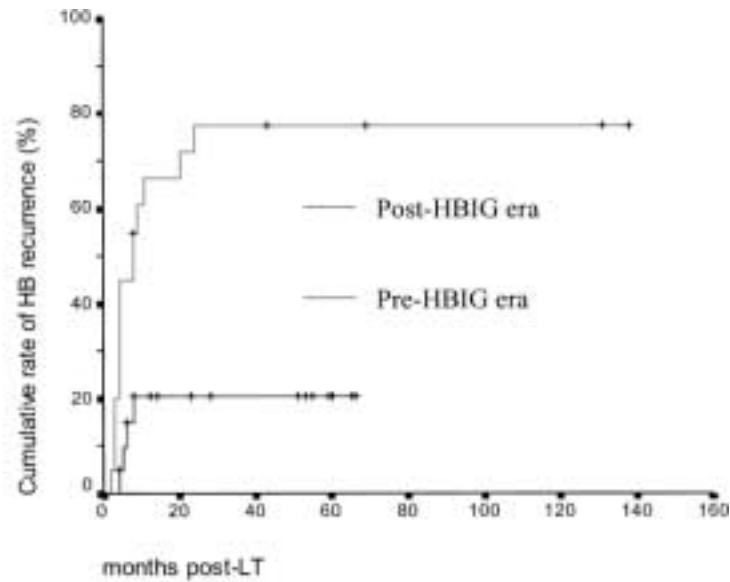


Figure 1. Kaplan-Meier curves showing rates of recurrent hepatitis B post-LT in patients who underwent LT in the pre-HBIG and post-HBIG eras.

Pre-HBIG No.	20	5	4	3	2	2	2
Post-HBIG No.	21	10	8	3			

era had features that predicted high risks for recurrent hepatitis B: 90% had cirrhosis, 74% were HBeAg positive, and 76% had detectable serum HBV DNA at listing; only 20% had HDV coinfection.

Median duration of post-LT follow-up in the pre-HBIG and post-HBIG eras was 76 months (range, 4 to 155 months) and 25 months (range, 4 to 68 months), respectively.

Recurrent Hepatitis B

In the pre-HBIG era, 15 patients (75%) developed recurrent hepatitis B: 13 patients experienced recurrence in the first year, and 2 patients, in the second year post-LT. In the post-HBIG era, only 4 patients (19%) developed recurrent hepatitis B, all 4 patients during the first year post-LT. Cumulative rates of recurrent

hepatitis B after 1, 3, and 5 years post-LT were 66%, 77%, and 77% among patients who underwent LT in the pre-HBIG era and 20%, 20%, and 20% among patients who underwent LT in the post-HBIG era ($P < .001$; Fig. 1). None of the 4 patients administered combination prophylaxis of IV HBIG and lamivudine developed recurrent hepatitis B after a median of 17 months (range, 9 to 25 months) of post-LT follow-up. Thus, hepatitis B recurred in 4 of 17 patients (24%) administered HBIG monotherapy.

Factors Associated With Recurrent Hepatitis B in the Post-HBIG Era

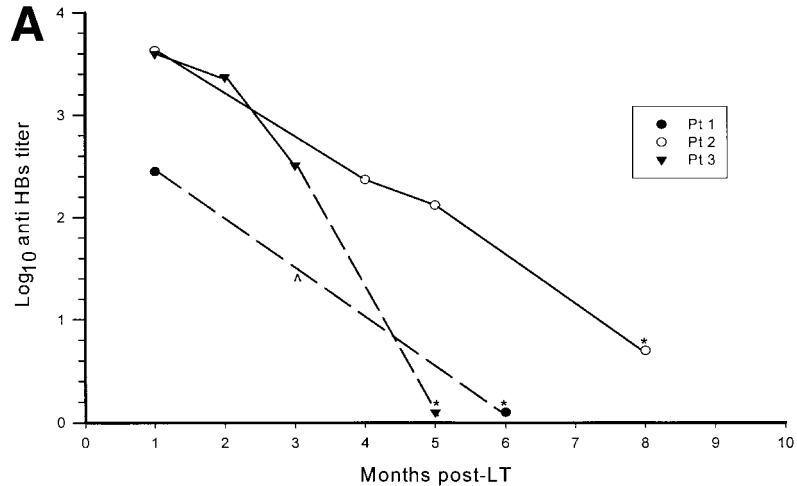
Anti-HBs titer was the most important factor associated with recurrent hepatitis B in the post-HBIG era. Of the 4 patients with recurrent hepatitis B, 2 patients missed

Table 2. Outcome of Patients Post-LT

	Pre-HBIG Era (n = 20)	Post-HBIG Era (n = 21)	P
Median duration of post-LT follow-up (mo)	76	25	<.05
Recurrent hepatitis B	15 (75)	4 (19)	<.001
All-cause mortality	6	3	NS
Death related to recurrent hepatitis B	5	2	NS
No recurrent hepatitis B	5 (25)	17 (81)	<.001
All-cause mortality	3	3	NS

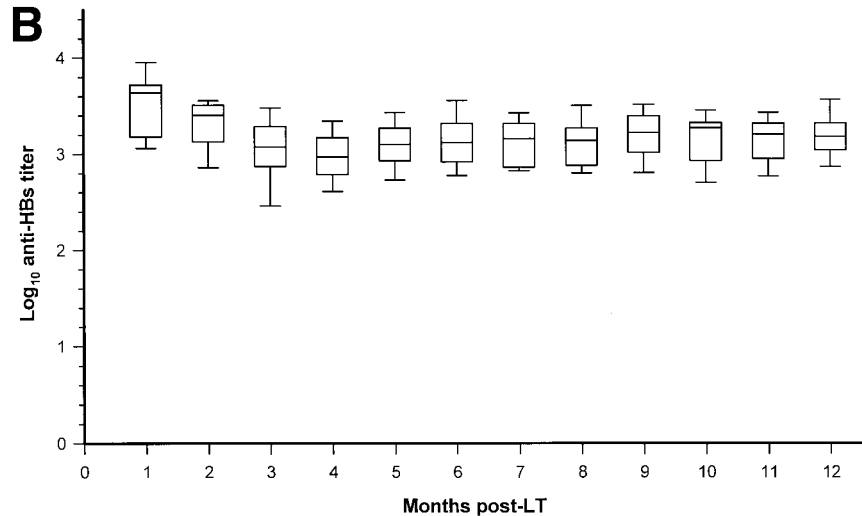
NOTE. Values expressed as number of patients (percent) unless stated otherwise.
Abbreviation: NS, not significant.

Figure 2. (A) Sequential anti-HBs titer (\log_{10} values, IU/L) of the 4 patients who developed recurrent hepatitis B despite IV HBIG.



* HB recurrence ^ : Missed HBIG dose
Pt 4 did not have anti-HBs data, missed M2 dose, and hepatitis B recurred in M4

Figure 2. (B) Sequential anti-HBs titer (\log_{10} values, IU/L) during the first year post-LT in the 17 patients administered IV HBIG who did not have recurrent hepatitis B. Box plots indicate 75th percentile, median, and 25th percentile values, the wickers indicate the highest and lowest values.



1 dose of HBIG during the first 3 months post-LT and hepatitis B recurred during months 4 and 6 post-LT. The other 2 patients were not able to maintain an anti-HBs titer greater than 100 IU/L after the first 4 months despite strict adherence to the HBIG protocol, and hepatitis B recurred during months 5 and 8 post-LT (Fig. 2A). In the remaining 17 patients with no recurrence, lowest trough anti-HBs titers during months 0 to 3, 4 to 6, and 7 to 12 post-LT were 217, 417, and 515 IU/L, respectively (Fig. 2B). Despite wide variation in anti-HBs titers during the first year, a stable anti-HBs titer greater than 500 IU/L was maintained in all uninfected patients after the first year post-LT.

In the post-HBIG era, data on HBeAg and HBV DNA at presentation were available for 19 patients. None of the 6 patients who were HBeAg and HBV

DNA negative at presentation developed recurrent hepatitis B compared with 3 of 13 patients (23%) who were HBeAg and/or HBV DNA positive at presentation. HBeAg and HBV DNA results at presentation were not available in the fourth patient who developed recurrent hepatitis B.

Treatment and Outcome of Patients With Recurrent Hepatitis B

Of the 15 patients who underwent LT in the pre-HBIG era who developed recurrent hepatitis B, 6 patients died 4 to 30 months (median, 14 months) post-LT (Table 2). Five patients died of causes related to recurrent hepatitis B: 3 patients of progressive liver failure 4, 9, and 12 months after the diagnosis of recurrent hepatitis B, and 2 patients of postoperative complications after

Table 3. Effect of Lamivudine Treatment in 9 Patients With Recurrent Hepatitis B Post-LT

Patient No.	Time to Recurrence (mo post-LT)	Pre-Lamivudine Treatment										Last Visit				
		Interval Between Recurrence and Lamivudine Treatment (mo)					Duration of Treatment (mo)					Last Visit				
		HBsAg	HBV-DNA	ALT (IU/L)	TB (mg/dL)	ALB (g/dL)	PT (s)	Histology	HBsAg	HBV-DNA	ALT (IU/L)	TB (mg/dL)	ALB (g/dL)	PT (s)		
1	24	(+)	(+)	145	0.9	3.4	13.2	Cirrhosis	(+)	(-)	68	1.2	3.9	10.6		
2	11	(+)	(+)	56	0.4	3.3	10.5	Cirrhosis	(-)	(-)	57	0.9	3.5	10.5		
3	4	(+)	(+)	148	2.7	3.5	12.3	Cirrhosis	(+)	(-)	77	1.1	3.6	10.3		
4	3	(+)	(+)	83	4.5	2.0	13.4	Cirrhosis	(+)	(+)	91	0.8	4.2	9.7		
5	8	(+)	(+)	294	12.5	2.6	11.9	Cirrhosis	(+)	(-)	53	3.9	3.4	9.9		
6	3	(+)	(-)	36	0.6	3.6	12.9	CHB	(+)	(-)	61	1.0	3.5	11.0		
7	3	(-)	(-)	41	1.4	2.7	13.8	Cirrhosis	(-)	(-)	36	0.8	3.7	10.7		
8	8	(+)	(+)	54	0.6	3.0	12.2	CHB	(+)	(+)	48	0.5	3.1	11.5		
9	4	(+)	(+)	73	0.9	2.4	10.0	CHB	(+)	(+)	120	1.1	3.5	10.3		

Abbreviations: CHB, chronic hepatitis B; ALT, alanine aminotransferase; TB, total bilirubin; ALB, albumin; PT, prothrombin time.

re-LT for recurrent hepatitis B. The sixth patient died of sepsis 26 months after the diagnosis of recurrent hepatitis B with normal graft function at the time of death. One patient was lost to follow-up 121 months after LT; liver biochemistry test results were normal during the last follow-up. Of the remaining 8 patients, 1 patient had normal graft function and undetectable serum HBV DNA 129 months after the diagnosis of recurrent hepatitis B. The other 7 patients were administered lamivudine treatment.

Of the 4 patients who underwent LT in the post-HBIG era who developed recurrent hepatitis B, 1 patient died of progressive graft failure 9 months post-LT, and 1 patient died of sepsis 2 months after re-LT for recurrent hepatitis B. The other 2 patients were administered lamivudine treatment.

Nine patients were administered lamivudine therapy (Table 3). The median duration of treatment was 28 months (range, 13 to 49 months). Six patients had histological cirrhosis before the onset of treatment. The interval from diagnosis of recurrent hepatitis B to initiation of lamivudine treatment varied from 2 to 131 months (median, 96 months). Eight patients were HBeAg positive and 7 patients had detectable serum HBV DNA before treatment. All patients had undetectable serum HBV DNA and improvement in liver biochemistry results within 6 months of treatment. However, only 1 patient cleared HBeAg and no patient cleared HBsAg. Three patients developed virological breakthroughs after 11, 12, and 19 months of lamivudine therapy. Two patients (no. 8 and 9) were confirmed to have mutations involving the YMDD motif of the polymerase gene. All 3 patients had slow deterioration in liver disease; 1 patient was started on adefovir dipivoxil treatment (patient 9) and 1 patient was maintained on lamivudine therapy only because of noncompliance and chronic renal insufficiency (patient 4), whereas the third patient died of a cerebrovascular accident (patient 8). Six patients had persistently undetectable serum HBV DNA and continued improvement in liver disease (Fig. 3) 13 to 49 months (median, 48 months) after the initiation of lamivudine treatment.

Discussion

In this study, we reported the outcome of patients with hepatitis B up to 14 years post-LT. We found that hepatitis B recurred in 75% of patients administered no prophylaxis or short-term low-dose HBIG and 19% of those administered long-term high-dose HBIG. These data are similar to previously published reports^{4,10-16} and support the use of high-dose IV HBIG in the pre-

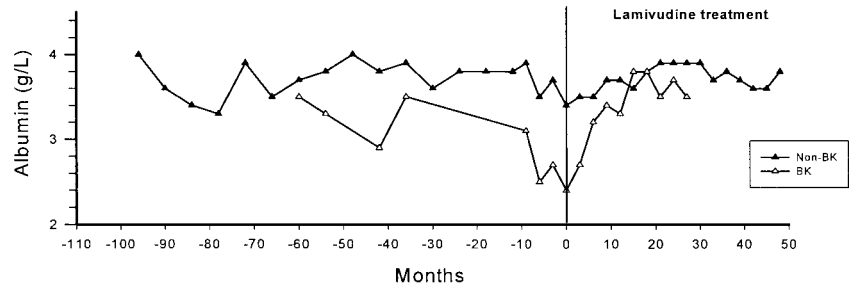
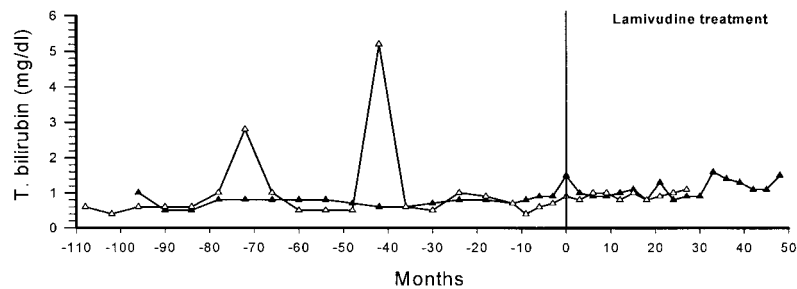
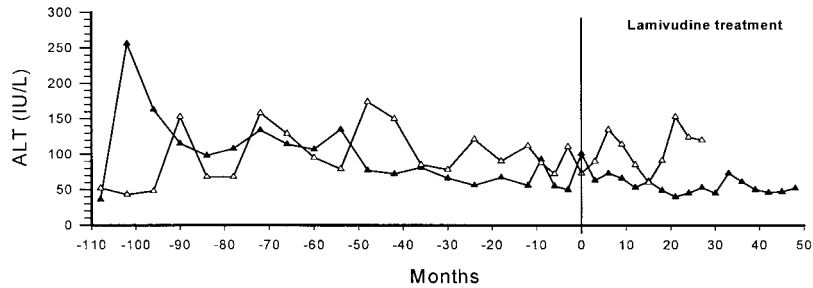


Figure 3. Serial values (median) of serum albumin, alanine aminotransferase, and total bilirubin in 9 patients administered lamivudine for recurrent hepatitis B. Biochemical values from the time recurrent hepatitis B was diagnosed were plotted to show changes before and after lamivudine treatment. (BK, virological breakthrough.)



vention of recurrent hepatitis B post-LT. Of the 4 patients who underwent LT in the post-HBIG era and developed recurrent hepatitis B, 3 of 3 patients tested were HBeAg positive and had detectable HBV DNA pre-LT. Two patients missed 1 dose of HBIG during the first 3 months post-LT, and 2 patients were unable to maintain anti-HBs titers greater than 100 IU/L despite strict adherence to a fixed-dose protocol. These data support the observations that (1) patients with a high viral load pre-LT have an increased risk for recurrent hepatitis B post-LT, (2) a fixed-dose regimen of HBIG administration may be insufficient in maintaining protective levels of anti-HBs in patients who are HBeAg and/or HBV DNA positive pre-LT, and (3) adequate anti-HBs titers must be maintained to prevent recurrent hepatitis B.^{4,15,16} Our data suggest that close monitoring of anti-HBs titer with supplemental HBIG when titers decrease to less than a protective level or more aggressive prophylactic regimen is needed for patients with a high viral load pre-LT. In accordance with other reports,²⁰⁻²³ none of our 4 patients adminis-

tered combination prophylaxis with HBIG and lamivudine developed recurrent hepatitis B after a median follow-up of 17 months.

We found most (89%) hepatitis B recurrence during the first year post-LT, and all recurrence within the first 2 years. These data suggest that despite the persistence of HBV DNA in the liver or extrahepatic reservoirs,^{14,26} neutralization of circulating virions and prevention of early graft infection when patients are heavily immunosuppressed may be the most important steps in the prevention of recurrent hepatitis B post-LT. Two of our patients who underwent LT in the pre-HBIG era had no evidence of reinfection up to 10 years after LT. Our findings suggest that prophylactic regimens may be tapered after the first 1 to 2 years post-LT because the risk for recurrent hepatitis B decreases. We are currently evaluating a tapering regimen in patients who have no evidence of recurrent hepatitis B after 1 year post-LT.

As in other studies,^{1,27} we found that patients with recurrent hepatitis B post-LT had rapidly progressive liver disease; 37% developed graft failure within 1 year,

and 78% of deaths were related to recurrent hepatitis B. The dismal outcome of patients with recurrent hepatitis B improved after lamivudine became available. Of the 9 patients administered lamivudine treatment, none died of graft failure after a median treatment duration of 28 months, although 6 patients had cirrhosis and 4 patients had mild hepatic decompensation when treatment was initiated. In accordance with other reports,^{24,28,29} all our patients had virological response, as well as clinical and biochemical improvement initially. Six patients with no breakthrough infection continued to have improved or stable liver disease up to 4 years after the initiation of lamivudine treatment. Of the 3 patients who developed virological breakthroughs, all had slow deterioration in liver disease. However, comorbid medical conditions and the addition of adefovir dipivoxil preclude us from determining the long-term effects of lamivudine-resistant HBV mutants in these patients.

In summary, our study showed that long-term high-dose IV HBIG is effective in preventing recurrent hepatitis B post-LT, especially in patients with a low viral load pre-LT or when anti-HBs titer was maintained at greater than 100 IU/L. We found that the risk for recurrent hepatitis B was very low after the first year post-LT. These data indicate that aggressive prophylaxis is needed during the initial post-LT period, especially in patients with a high viral load pre-LT, but the prophylactic regimen can be tapered with time. Our data showed that in patients with recurrent hepatitis B, lamivudine is effective in stabilizing or improving liver disease for up to 4 years, but the clinical benefits may be negated in patients with virological breakthrough infection.

References

- Demetris AJ, Todo S, Van Thiel DH, Fung JJ, Iwaki Y, Sysyn G, et al. Evolution of hepatitis B virus liver disease after hepatic replacement. Practical and theoretical considerations. *Am J Pathol* 1990;137:667-676.
- O'Grady JG, Smith HM, Davies SE, Daniels HM, Donaldson PT, Tan KC, et al. Hepatitis B virus reinfection after orthotopic liver transplantation. Serological and clinical implications. *J Hepatol* 1992;14:104-111.
- Eason JD, Freeman RB Jr, Rohrer RJ, Lewis WD, Jenkins R, Dienstag J, et al. Should liver transplantation be performed for patients with hepatitis B? *Transplantation* 1994;57:1588-1593.
- Samuel D, Muller R, Alexander G, Fassati L, Ducot B, Benhamou JP, et al. Liver transplantation in European patients with the hepatitis B surface antigen. *N Engl J Med* 1993;329:1842-1847.
- Lawchart W, Muller R, Pichlmayr R. Long-term immunoprophylaxis of hepatitis B reinfection in recipients of human liver allografts. *Transplant Proc* 1987;19:4051-4053.
- Perrillo RP, Mason AL. Hepatitis B and liver transplantation. Problems and promises. *N Engl J Med* 1993;329:1885-1887.
- Muller R, Samuel D, Fassati LR, Benhamou JP, Bismuth H, Alexander GJ. "EUROHEP" consensus report on the management of liver transplantation for hepatitis B virus infection. European Concerted Action on Viral Hepatitis. *J Hepatol* 1994; 21:1140-1143.
- Ghany MG, Ayola B, Villamil FG, Gish RG, Rojter S, Vierling JM, et al. Hepatitis B virus S mutants in liver transplant recipients who were reinfected despite hepatitis B immune globulin prophylaxis. *Hepatology* 1998;27:213-222.
- Protzer-Knolle U, Naumann U, Bartschlagler R, Berg T, Hopf U, Meyer zum Buschenfelde KH, et al. Hepatitis B virus with antigenically altered hepatitis B surface antigen is selected by high-dose hepatitis B immune globulin after liver transplantation. *Hepatology* 1998;27:254-263.
- Samuel D, Bismuth A, Mathieu D, Arulnaden JL, Reynes M, Benhamou JP, et al. Passive immunoprophylaxis after liver transplantation in HBsAg-positive patients. *Lancet* 1991;337:813-815.
- Lemmens HP, Langrehr JM, Blumhardt G, Lohmann R, Knoop M, Verschl J, et al. Outcome following orthotopic liver transplantation in HBsAg-positive patients using short- or long-term immunoprophylaxis. *Transplant Proc* 1994;26:3622-3623.
- Langrehr JM, Lemmens HP, Keck H, Lohmann R, Knoop M, Neumann U, et al. Liver transplantation in hepatitis B surface antigen positive patients with postoperative long-term immunoprophylaxis. *Transplant Proc* 1995;27:1215-1216.
- Grazi GL, Mazziotti A, Sama C, Jovine E, Stefanini F, Paladini R, et al. Liver transplantation in HBsAg-positive HBV-DNA-negative cirrhotics: Immunoprophylaxis and long-term outcome. *Liver Transpl Surg* 1996;2:418-425.
- Terrault NA, Zhou S, Combs C, Hahn JA, Lake JR, Roberts JP, et al. Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. *Hepatology* 1996; 24:1327-1333.
- McGory RW, Ishitani MB, Oliveira WM, Stevenson WC, McCullough CS, Dickson RC, et al. Improved outcome of orthotopic liver transplantation for chronic hepatitis B cirrhosis using aggressive passive immunization. *Transplantation* 1996; 61:1358-1364.
- Sawyer RG, McGory RW, Gaffey MJ, McCullough CC, Shephard BL, Houlgrave CW, et al. Improved clinical outcome with liver transplantation for hepatitis B-induced chronic liver failure using passive immunization. *Ann Surg* 1998;227:841-850.
- Grellier L, Multimer D, Ahmed M, Brown D, Burroughs AK, Rolles K, et al. Lamivudine prophylaxis against reinfection in liver transplantation for hepatitis B cirrhosis. *Lancet* 1996;348: 1212-1215.
- Perrillo RP, Wright T, Rakela J, Levy G, Schiff E, Gish R, et al. A multi-center United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. *Hepatology* 2001;33:424-432.
- Mutimer DJ, Pillay D, Dragon E, Tang H, Ahmed M, O'Donnell K, et al. High pre-treatment serum hepatitis B virus titre predicts failure of lamivudine prophylaxis and graft re-infection after liver transplantation. *J Hepatol* 1999;30:715-721.
- Markowitz JS, Martin P, Conrad AJ, Markmann JF, Seu P, Yersiz H, et al. Prophylaxis against hepatitis B recurrence following liver transplantation using combination lamivudine and hepatitis B immune globulin. *Hepatology* 1998;28:585-589.

21. Yao YF, Osorio RW, Roberts JP, Poordad FF, Briceno MN, Garcia-Kennedy R, et al. Intramuscular hepatitis B immune globulin combined with lamivudine for prophylaxis against hepatitis B recurrence after liver transplantation. *Liver Transpl Surg* 1999;5:491-496.
22. Yoshida EM, Erb SR, Partovi N, Scudamore CH, Chung SW, Frighetto L, et al. Liver transplantation for chronic hepatitis B infection with the use of combination lamivudine and low-dose hepatitis B immune globulin. *Liver Transpl Surg* 1999;5:520-525.
23. Angus PW, McCaughan GW, Gane EJ, Crawford DHG, Harley H, Australasian Liver Transplant Study Group. Combination low-dose hepatitis B immune globulin and lamivudine therapy provides effective prophylaxis against post-transplantation hepatitis B. *Liver Transpl* 2000;6:429-433.
24. Perrillo R, Rakela J, Dienstag J, Levy G, Martin P, Wright T, et al. Multicenter study of lamivudine therapy for hepatitis B after liver transplantation. *Hepatology* 1999;29:1581-1586.
25. Lok ASF, Hussain M, Cursano C, Margotti M, Gramenzi A, Grazi GL, et al. Evolution of hepatitis B virus polymerase gene mutations in hepatitis B e antigen negative patients receiving lamivudine therapy. *Hepatology* 2000;32:1145-1153.
26. Feray C, Zignego AL, Samuel D, Bismuth A, Reynes M, Tiollais P, et al. Persistent hepatitis B virus infection of mononuclear blood cells without concomitant liver infection. The liver transplantation model. *Transplantation* 1990;49:1155-1158.
27. Todo S, Demetris AJ, Van Thiel D, Teperman L, Fung JJ, Starzl TE. Orthotopic liver transplantation for patients with hepatitis B virus related liver disease. *Hepatology* 1991;13:619-626.
28. Nery JR, Weppler D, Rodriguez M, Ruiz P, Schiff ER, Tzakis AG. Efficacy of lamivudine in controlling hepatitis B virus recurrence after liver transplantation. *Transplantation* 1998;65:1615-1621.
29. Malkan G, Cattral MS, Humar A, Asghar HA, Greig PD, Hemming AW, et al. Lamivudine for hepatitis B in liver transplantation. *Transplantation* 2000;69:1403-1407.