Effect of Lamivudine Treatment on Survival of 309 North American Patients Awaiting Liver Transplantation for Chronic Hepatitis B

Robert J. Fontana,[*] Emmet B. Keeffe,[†] William Carey,[‡] Michael Fried,[§] Rajender Reddy,[‖] Kris V. Kowdley,[¶] Consuelo Soldevila-Pico,[#] Leslie A. McClure,[*] and Anna S.F. Lok[*] for the National Institutes of Health Hepatitis B Virus Orthotopic Liver Transplantation Study Group

The primary aim of this study is to determine whether treatment with lamivudine improved pre–liver transplantation (pre-LT) and LT-free survival of patients awaiting LT for hepatitis B virus (HBV)-related cirrhosis. Data from 162 lamivudine-treated and 147 untreated transplant candidates managed at 20 North American transplant centers between 1996 and 1998 were collected and compared. Lamivudine-treated patients were more likely to be men, hepatitis B e antigen positive, HBV DNA positive, and have lower serum albumin levels at listing ($P < .05$). Actuarial pre-LT and LT-free survival were similar in lamivudine-treated and untreated patients. Using Cox regression analysis, the only significant predictor of pre-LT patient survival was the modified Child-Turcotte-Pugh (mCTP) score, whereas significant predictors of LT-free survival included ethnic background, lamivudine treatment, indication for LT, baseline serum alanine aminotransferase level, and baseline mCTP score. Lamivudine had no apparent effect on liver disease severity in patients undergoing LT, but appeared to improve disease severity in patients still awaiting LT. Breakthrough infection was noted in 11% of lamivudine-treated patients. We conclude that lamivudine therapy is not associated with improved pre-LT or LT-free survival in LT candidates with chronic hepatitis B. However, a subset of patients with less advanced liver failure may derive clinical benefit from lamivudine therapy, thus delaying the need for LT. In the absence of prospective, randomized, controlled trials of lamivudine in patients with decompensated cirrhosis, careful selection of patients and optimal timing of treatment are needed to balance the risk versus benefit of lamivudine therapy in LT candidates. (*Liver Transpl 2002;8:433-439.*)

Mortality caused by hepatitis B virus (HBV)-related liver disease in the United States is approximately 5,000 deaths/yr.[1] The outcome of patients with chronic hepatitis B after liver transplantation (LT) has significantly improved in the last decade; however, less than 300 hepatitis B surface antigen (HBsAg)-positive patients undergo LT in the United States each year because of the critical shortage of donor organs.[2,3] As the waiting time for LT increases, clinicians are challenged to manage patients with decompensated HBV-related cirrhosis for longer periods.

Lamivudine, a potent nucleoside analogue, is currently approved for the treatment of patients with chronic hepatitis B.[4] Small, uncontrolled, open-label studies have shown that lamivudine can lead to improvement in both laboratory and clinical liver disease parameters in patients with decompensated hepatitis B cirrhosis.[5-8] In some of these series, lamivudine treatment was reported to markedly improve liver function and reduce the need for LT.[5-8] However, breakthrough infection may occur during prolonged treatment with lamivudine because of the emergence of drug-resistant mutants.[9] Although lamivudine-resistant HBV mutants have decreased replication fitness compared with wild-type virus, flares in liver disease activity and hepatic decompensation have been reported with breakthrough infection.[10,11] In addition, patients with lamivudine-resistant mutants may have an increased risk for recurrent hepatitis B post-LT.[11,12] Therefore, the optimal time to initiate lamivudine treatment in HBsAg-positive LT candidates and the overall benefit of therapy in these patients remain unclear.

*From the *Departments of Internal Medicine and Biostatistics, University of Michigan Medical Center, Ann Arbor, MI; †Stanford University Medical Center, Stanford, CA; ‡Cleveland Clinic Hospitals, Cleveland, OH; §University of North Carolina, Chapel Hill, NC; ‖University of Miami, Miami, FL; ¶University of Washington, Seattle, WA; and the #University of Florida, Gainesville, FL.*

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Address reprint requests to Anna S.F. Lok, MD, 3912 Taubman Center, Ann Arbor, MI 48109-0362. Telephone: 734-936-4780; FAX: 734-936-7392; E-mail: aslok@umich.edu

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The primary aim of this study is to determine whether lamivudine treatment improves pre-LT survival or delays or obviates the need for LT in patients with HBV-related cirrhosis. The secondary aim is to assess the outcome of patients who developed breakthrough infection during lamivudine therapy. Results of this retrospective analysis of 309 HBsAg-positive LT candidates treated at 20 North American transplant centers before Food and Drug Administration approval of lamivudine for chronic hepatitis B are presented.

Methods

Investigators from 20 North American (18 American and 2 Canadian) LT centers were asked to complete a written survey on each adult patient listed for LT for HBV-related liver disease between January 1996 and June 1998.[13] Demographic, virological, and laboratory data, as well as clinical outcomes, were obtained through a retrospective review of patient medical records and the transplant database under local institutional review board guidelines. Sixteen patients with HBV-related acute liver failure were excluded. Data for 309 patients with HBsAg-positive cirrhosis or hepatocellular carcinoma (HCC) followed up through May 2000 form the basis of this report.

Data Collection

Subject age, sex, ethnic background, indication for LT (cirrhosis or HCC), clinical status at last available follow-up (LT, death, still waiting, delisted), date of LT, and use of antiviral medications pre-LT were recorded. The following virological values were obtained at the time of listing and at LT or most recent pre-LT follow-up visit: HBsAg, hepatitis B e antigen (HBeAg), antibody to HBeAg, antibody to hepatitis C virus (HCV), antibody to hepatitis delta virus, and HBV DNA. In addition, the following laboratory parameters were obtained at the same times: serum aspartate aminotransferase, alanine aminotransferase (ALT), bilirubin, and albumin levels and prothrombin time. Time to development of lamivudine resistance, defined as reemergence of previously undetectable HBV DNA in a patient administered lamivudine, also was recorded.

Hepatitis serological parameters were tested using commercially available enzyme immunoassays (Abbott Laboratories, N Chicago, IL). Serum HBV DNA was tested at each center using liquid hybridization (Abbott Laboratories), branched-chain DNA (Chiron/Bayer, Emeryville, CA), or hybrid capture assays (Digene, Gaithersburg, MD).

Liver Disease Severity

Before 1998, Child-Turcotte-Pugh (CTP) scores were not required to prioritize patients on the liver transplant waiting list. During chart review, we noted that the presence and extent of hepatic encephalopathy and ascites were not reliably available. Therefore, severity of liver disease was estimated using three of the five CTP laboratory criteria. Scores for albumin and bilirubin levels and either international normalized ratio or prothrombin time were added and reported as the modified CTP (mCTP) score, with a range from 3 to 9 points. To account for missing baseline mCTP scores in the regression model, an imputed mCTP score was calculated for patients with missing baseline values by taking the average score of the variables for which data were recorded (i.e., albumin, bilirubin, prothrombin time) and multiplying by three. Proportions of patients with complete baseline laboratory data were 95%, 96%, and 93% for albumin, bilirubin, and prothrombin time, respectively.

Data Analysis

Primary outcomes of the study were pre-LT and LT-free survival. Data were entered into an SPSS version 9.0 Windows 97 database (SPSS Inc, Chicago, IL). Descriptive statistics were calculated and are reported as mean ± SE unless indicated otherwise. Demographic, laboratory, and clinical parameters at baseline, LT, and last follow-up were compared between patients administered lamivudine pre-LT (group 1) and those who were not treated (group 2) by using *t*-tests for continuous variables and Chi-squared analysis or Fisher's exact test for categorical variables. Survival curves were estimated using the Kaplan-Meier method and compared by log-rank test. Univariate and multivariate Cox regression analyses were performed to identify factors associated with pre-LT patient survival and LT-free patient survival. Patients were censored at the time of LT, death, or last available follow-up for analysis of LT-free survival. Baseline covariates significant at the .10 level or less in univariate modeling were included in the multivariate Cox regression model. The following factors were tested as predictors of both pre-LT survival and LT-free survival: age, sex, ethnicity, indication for LT, serum ALT level at listing, HBeAg/HBV DNA at listing, mCTP score at listing, HCV serological status, and use of lamivudine. P less than .05 is considered statistically significant.

Results

Study Population

Of 309 patients studied, 162 patients (group 1) were administered antiviral therapy consisting of lamivudine alone (159 patients), lamivudine and famciclovir (2 patients), or famciclovir alone (1 patient), whereas 147 patients (group 2) were not administered lamivudine pre-LT. At the time of listing, the two groups were similar in age, ethnic background, prevalence of HCV and hepatitis delta virus coinfection, and indications for LT (Table 1). However, group 1 patients were significantly more likely to be men and have detectable HBeAg or HBV DNA than group 2 patients. In addi-

Table 1. Clinical Characteristics of the Study Population

	LAM Treatment (n = 162)	No LAM Treatment (n = 147)	*P*
Sex			
Men	137 (85)	110 (75)	.033
Women	25 (15)	37 (25)	
Age (yr)	50.8 ± 0.8	50.3 ± 0.8	.601
Ethnicity			
White	89 (55)	74 (50)	.671
Asian	62 (38)	59 (40)	
Black	4 (3)	7 (5)	
Other	7 (4)	7 (5)	
Indications for LT			
Cirrhosis	145 (90)	124 (85)	.178
HCC	17 (10)	23 (15)	
	At listing		
Viral serology			
HBeAg+	61/118 (52)	27/91 (30)	.001
HBV DNA+	71/125 (57)	32/99 (32)	.001
Anti-HCV+	15/133 (11)	16/114 (14)	.635
Anti-HDV+	8/58 (14)	8/33 (24)	.208
Laboratory values			
ALT (IU/L)	125 ± 16	117 ± 15	.730
Albumin (g/dl)	2.9 ± 0.05	3.1 ± 0.07	.013
Bilirubin (mg/dl)	5.2 ± 0.6	5.6 ± 0.7	.700
PT (INR)	1.6 ± 0.05	1.7 ± 0.1	.405
mCTP score	6.0 ± 0.15	5.7 ± 0.2	.163

NOTE. Data expressed as number (percent) or mean ± SE. HBV DNA testing was performed at local sites.
Abbreviations: PT, prothrombin time; INR, international normalized ratio; anti-HCV, antibody to HCV; anti-HDV, antibody to hepatitis delta virus; LAM, lamivudine.

tion, group 1 patients had significantly lower serum albumin levels. Mean duration of pre-LT follow-up to predetermined study end points of death, LT, or last available visit in non–transplant recipients was significantly greater in group 1 compared with group 2 patients (10.2 ± 0.75 *v* 7.2 ± 0.62 months; $P = .002$). At the time of data analysis, 175 patients (57%) had undergone LT (Fig. 1). Of the remaining patients, 87 patients (28%) were still awaiting LT, 28 patients (9%) had died, and 19 patients (6%) had been removed from the waiting list.

Pre-LT and LT-Free Survival

Actuarial pre-LT patient survival of the 162 lamivudine-treated and 147 untreated patients was similar ($P = .529$; Fig. 2). In univariate and multivariate Cox regression analysis, the only covariate significantly associated with death before LT was mCTP score (hazard ratio, 1.60; 95% confidence interval, 1.3 to 2.0; $P =$

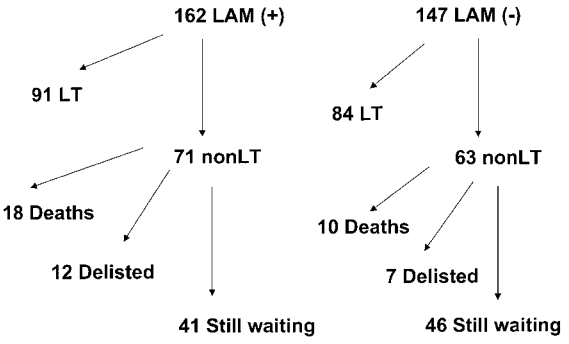

Figure 1. Disposition of the 162 lamivudine (LAM)-treated and 147 untreated patients during the study.

.0001). Specifically, for each one-unit increase in mCTP score, the hazard for death increased by 60%. However, note that there were only 28 deaths during the course of the study, which limited the ability to estimate the effect of several covariates on pre-LT survival.

A plot of actuarial LT-free survival showed that although lamivudine-treated patients tended to have improved LT-free survival, the difference was not statistically significant ($P = .09$; Fig. 3). On both univariate and multivariate Cox regression analyses, lamivudine treatment, ethnicity, HCC as the indication for LT, baseline serum ALT level, and mCTP score were significant predictors of LT-free survival (Table 2). More specifically, for each increase in baseline serum ALT level by 10 IU/L, there was a 1% increase in the

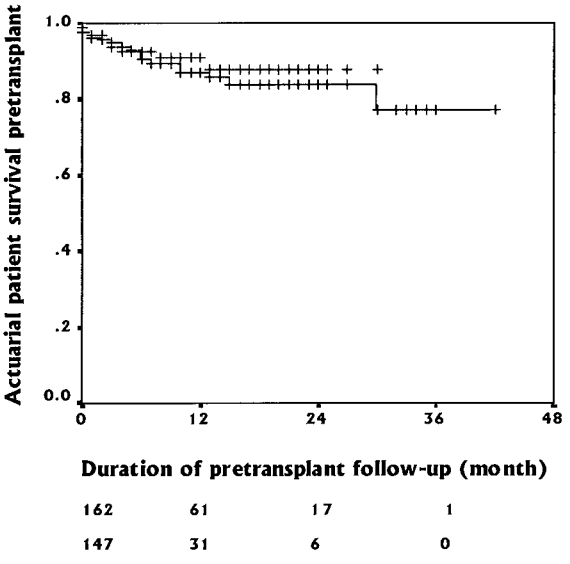

Figure 2. Actuarial pre-LT survival of 162 lamivudine-treated group 1 patients (—) was similar to that of 147 untreated group 2 patients (- - -). $P = .53$, log-rank test.

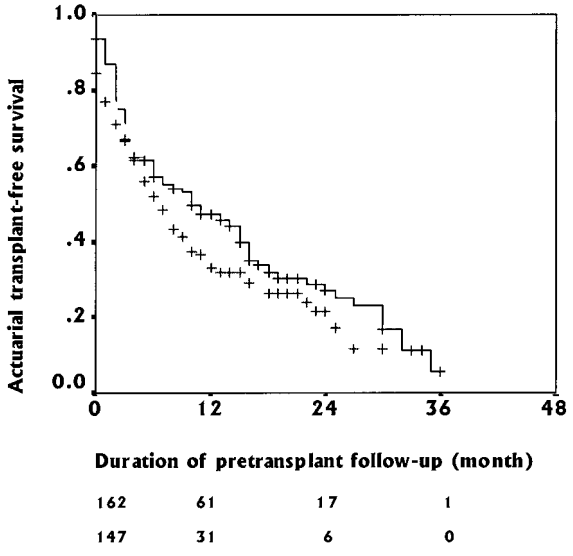

Figure 3. Actuarial LT-free survival of 162 lamivudine-treated group 1 patients (—) was not significantly different from that of 147 untreated group 2 patients (- - -). $P = 0.09$, log-rank test.

hazard for death or LT. Similarly, for each increase in mCTP score by one point, there was a 37% increase in the hazard for death or LT.

Effect of Lamivudine on Liver Disease

Transplant recipients. At the time of data analysis, 91 group 1 patients (56%) and 84 group 2 patients (57%) had undergone LT (Fig. 1). Mean subject age (50.5 ± 1.1 *v* 52.1 ± 1.1 years), ethnic background (54% *v* 54% white), and indications for LT (82% *v* 83% cirrhosis) were similar in group 1 and group 2 transplant recipients, respectively. However, as in the entire study population, group 1 transplant recipients were more likely to be men (87% *v* 74%; $P = .03$) and have a longer duration of pre-LT follow-up than group 2 transplant recipients (8.1 ± 0.9 *v* 5.4 ± 0.7 months; $P = .02$). At listing, group 1 patients were more likely to have detectable HBV DNA; however, other liver disease severity parameters were similar to those in group 2 patients (Table 3).

At LT, the proportion of group 1 patients with detectable HBV DNA had decreased compared with baseline. However, other laboratory values reflecting liver disease severity were essentially unchanged, and mCTP scores in lamivudine-treated and untreated patients were similar at the time of LT.

Non–transplant recipients. Seventy-one lamivudine-treated patients (44%) and 63 untreated patients (43%) had not undergone LT (Fig. 1). Mean duration of pre-LT follow-up was longer in group 1 than group 2 patients not undergoing LT (12.9 ± 1.2 *v* 9.5 ± 1.1 months; $P = .04$). Eighteen lamivudine-treated patients (11%) and 10 untreated patients (7%) died while awaiting LT. Twelve lamivudine-treated patients (7%) and 7 untreated patients (5%) were removed from the LT waiting list, primarily because of non–liver-related causes, including relocation, insurance issues, noncompliance, and development of significant pulmonary hypertension.

At the time of data analysis, 41 lamivudine-treated and 46 untreated patients were still awaiting LT (Table 3). Mean subject age (52.6 ± 1.4 *v* 48.8 ± 1.3 years), ethnicity (51% *v* 48% white), and sex (83% *v* 80% men) were similar in group 1 and group 2 patients,

Table 2. Univariate and Multivariate Cox Regression Model of LT-Free Survival

Variable	Univariate Hazard Ratio* (95% CI)	Univariate *P*	Multivariate Hazard Ratio† (95% CI)	Multivariate *P*
Lamivudine treatment	0.78 (0.59-1.04)	.09	0.68 (0.50-0.91)	.010
Race‡		.038		.049
Black	0.84 (0.62-1.13)		0.7 (0.52-0.97)	
Asian	1.25 (0.61-2.6)		0.92 (0.44-1.9)	
Other	2.34 (1.3-4.3)		1.76 (0.9-3.4)	
Indication for LT (cirrhosis)	1.41 (0.95-2.1)	.086	1.69 (1.1-2.6)	.016
Baseline serum ALT	1.001 (1.001-1.002)	.0006	1.001 (1.0-1.002)	.0042
Baseline mCTP§	1.37 (1.3-1.5)	.0001	1.36 (1.3-1.5)	.0001

Abbreviations: CI, confidence interval.
*Controlled for lamivudine treatment.
†Controlled for all other covariates in the model.
‡Reference group is white.
§Imput as described in Methods.

Table 3. Clinical Characteristics of Transplant Recipients and Those Still Awaiting LT

	Transplant Recipients			Still Awaiting LT		
	LAM Treatment (n = 91)	No LAM Treatment (n = 84)	*P*	LAM Treatment (n = 41)	No LAM Treatment (n = 46)	*P*
			At listing			
Viral serology						
HBeAg positive	29/70 (41)	19/56 (34)	.389	16/26 (62)	6/25 (24)	.007
HBV DNA positive	37/72 (51)	16/58 (27)	.006	18/29 (62)	11/30 (37)	.051
Laboratory values						
ALT (IU/L)	131 ± 26	142 ± 25	.757	122 ± 22	78 ± 13	.093
Albumin (g/dL)	2.8 ± 0.06	2.9 ± 0.1	.221	3.2 ± 0.1	3.4 ± 0.1	.091
Bilirubin (mg/dL)	5.8 ± 1.0	7.6 ± 1.2	.227	2.9 ± 0.5	1.8 ± 0.2	.054
PT (INR)	1.7 ± 0.07	1.9 ± 0.1	.148	1.6 ± 0.08	1.4 ± 0.05	.206
mCTP	6.1 ± 0.2	6.2 ± 0.2	.715	5.4 ± 0.3	4.7 ± 0.3	.084
			At LT or last follow-up			
Viral serology						
HBeAg±	17/60 (28)	10/33 (30)	.841	7/14 (50)	3/9 (33)	.431
HBV DNA±	14/71 (20)	11/40 (27)	.346	4/24 (17)	8/18 (44)	.049
Laboratory values						
ALT (IU/L)	104 ± 27	124 ± 20	.552	56.5 ± 10.3	60.5 ± 6.5	.742
Albumin (g/dl)	3.0 ± 0.07	3.0 ± 0.08	.970	3.5 ± 0.1	3.4 ± 0.1	.808
Bilirubin (mg/dl)	6.4 ± 1.1	9.8 ± 1.5	.060	1.7 ± 0.2	2.4 ± 0.6	.199
PT (INR)	1.9 ± 0.3	2.2 ± 0.3	.500	1.4 ± 0.06	1.5 ± 0.06	.087
mCTP	6.1 ± 0.2	6.3 ± 0.3	.564	4.7 ± 0.3	5.3 ± 0.4	.163

NOTE. Data expressed as number (percent) or mean ± SE.
Abbreviations: PT, prothrombin time; INR, international normalized ratio.

respectively. However, cirrhosis as the indication for LT (97% *v* 85%; $P = .039$), duration of pre-LT follow-up (16.1 ± 1.5 *v* 11.0 ± 1.4 months; $P = .013$), and presence of detectable HBeAg and HBV DNA at listing was greater in group 1 compared with group 2 patients, respectively.

At the last follow-up visit, the proportion of group 1 patients with detectable HBV DNA had decreased compared with baseline and was significantly lower compared with group 2 patients ($P = .049$). In addition, although group 1 patients had a trend toward higher serum bilirubin levels and mCTP scores at listing, these differences were no longer apparent at the most recent visit, suggesting that lamivudine may have improved or stabilized liver disease severity in group 1 patients.

Breakthrough Infection

Six transplant recipients and 12 non–transplant recipients developed breakthrough infection after a median of 12 months of lamivudine treatment (range, 4 to 42 months). Of the 12 non–transplant recipients, 1 patient died of progressive liver failure 3 months after the development of breakthrough infection and 5 patients were removed from the waiting list for various reasons, including worsening liver function in 1 patient. A paired comparison of listing and last available pre-LT mCTP scores in 9 of the 18 patients with breakthrough infection shows that 4 patients had an increase greater than 2 points, 1 patient had a reduction greater than 2 points, and 4 patients had a change in mCTP score less than 2 points.

Of the six patients with breakthrough infection undergoing LT, four patients were administered a combination of hepatitis B immune globulin (HBIG) and lamivudine, one patient was administered HBIG alone, and one patient was administered lamivudine alone post-LT. During a median post-LT follow-up of 11 months (range, 1 to 25 months), one patient administered combination prophylaxis followed by lamivudine monotherapy developed recurrent hepatitis B. The other five patients have remained HBsAg negative, with normal serum ALT levels.

Discussion

In this retrospective analysis of 309 HBsAg-positive patients listed for LT at 20 North American transplant

centers, we found that 52% of patients were administered lamivudine pre-LT. Patient selection for lamivudine treatment and the decision to proceed with LT were determined by local investigators. All patients on this study were listed for LT before the approval of lamivudine as a treatment for chronic hepatitis B. Patients who were HBeAg and/or serum HBV DNA positive at listing were more likely to be treated with lamivudine. Contrary to previous reports of uncontrolled studies in small numbers of patients, our large retrospective study failed to show a significant improvement in pre-LT or LT-free survival with lamivudine treatment.[6-8]

We acknowledge that our study is based on retrospective data, and treatment was not randomized. However, we are confident that data for survival and LT are accurate and complete. In addition, follow-up information and the proportion of patients removed from the transplant waiting list were similar in the two groups. It is possible that a greater prevalence of HBV replication markers among the lamivudine-treated group may have biased the results against treatment. Our results also may be biased because patients administered lamivudine had lower serum albumin levels at listing (Table 1). However, other laboratory markers of liver disease severity (bilirubin, prothrombin time, and mCTP score) were similar between the two groups. Cox regression analyses showed that only mCTP score at listing was significantly associated with pre-LT survival. Baseline mCTP score was the strongest predictor of LT-free survival; however, other factors, including baseline ALT level, lamivudine treatment, indication for LT, and race also were significant predictors of LT-free survival (Table 2). The clinical importance of race in predicting survival is unclear because there were only 14 patients of "other" ethnicity. Although it would be of interest to test the recently proposed Model for End-Stage Liver Disease score as a predictor of pre-LT survival, the retrospective nature of our study with incomplete baseline data capture precluded us from doing so.[14,15]

Findings of this study are consistent with other studies showing the importance of liver disease severity in predicting patient survival in lamivudine-treated patients with decompensated HBV-related cirrhosis.[16] Our data suggest that lamivudine treatment may delay the need for LT in some patients with HBsAg-positive cirrhosis or HCC, but it does not improve overall pre-LT survival.

Among transplant recipients, lamivudine treatment decreased HBV replication, but had no appreciable effect on liver disease severity (Table 3). Conversely, among patients still awaiting LT, lamivudine treatment appeared to improve or stabilize liver disease, reflected by a decrease in mCTP scores among treated patients compared with an increase in mCTP scores among untreated patients (Table 3). The difference in clinical benefit between patients still awaiting LT and those who underwent LT who were administered lamivudine may be related to less advanced liver failure at listing (baseline mean mCTP scores, 5.4 *v* 6.1) and longer mean duration of treatment (16.1 *v* 8.1 months) in patients still awaiting LT. Our observations are consistent with previous reports showing that clinical benefit with lamivudine treatment takes at least 3 to 6 months.[5,6,8,16] Thus, patients with very advanced liver failure may not derive a benefit from lamivudine treatment and should be prioritized for LT.

Breakthrough infection was reported in 18 patients (11%) after a median of 12 months of lamivudine treatment. Although serum HBV DNA was monitored using different assays at varying intervals in participating centers, the rate of breakthrough infection observed in this study is similar to that reported in other studies.[16,17] Because of the lack of stored samples for analysis, we could not confirm whether all patients with breakthrough infection had lamivudine-resistant HBV mutants.[9] Of the 12 patients who did not undergo LT, 1 patient died of progressive liver failure and 1 patient was removed from the waiting list because of worsening liver disease. Detailed data on 9 of the 18 patients with breakthrough infection showed that at least 4 patients had an increase in mCTP score by 2 points. Although mCTP score has not been validated as a reliable predictor of pre-LT mortality, these findings are concerning because with time, an increasing proportion of patients develop lamivudine resistance. Of the 6 patients who underwent LT, only 1 patient developed recurrent hepatitis B. Recurrence in this patient coincided with a switch from combination prophylaxis to lamivudine monotherapy. Longer follow-up of remaining patients is needed to determine whether HBIG alone or in combination with lamivudine can prevent recurrent hepatitis B.[10,12,17]

Our study represents the largest reported experience of North American patients awaiting LT for HBsAg-positive cirrhosis or HCC. We found that lamivudine was administered pre-LT in 52% of HBsAg-positive LT candidates listed between 1996 and 1998. It is likely that with the Food and Drug Administration approval of lamivudine in 1998, its use in this patient population may have increased, although the approved indication does not include patients with decompensated cirrhosis. Contrary to previous reports, we found that lamivudine treatment did not improve overall pre-LT or LT-free survival. However, our data suggest that a subset of patients with less advanced liver failure may derive

clinical benefit from lamivudine treatment, thus delaying the need for LT.

Breakthrough infection occurred in 11% of lamivudine-treated patients. Based on our data and other published reports, in general, the short-term outcome of patients with lamivudine resistance is favorable, but some patients may develop rapidly progressive liver failure before a donor liver becomes available, whereas others may develop recurrent hepatitis B despite HBIG prophylaxis.[11,12,17] Adefovir dipivoxil has been reported to have in vitro and in vivo effect on inhibiting wild-type and lamivudine-resistant HBV; however, its long-term safety and efficacy in patients with decompensated cirrhosis or recurrent hepatitis B post-LT remain to be established.[18] Thus, in the absence of prospective, randomized, controlled trials of lamivudine in patients with decompensated cirrhosis, careful selection of patients and optimal timing of treatment is needed in HBsAg-positive LT candidates to derive the maximum benefit from lamivudine treatment.

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References

1. Margolis HS, Alter MJ, Hadler SC. Hepatitis B: Evolving epidemiology and implications for control. Semin Liver Dis 1991;11: 84-92.
2. Annual Report of the US Scientific Registry for Organ Sharing and the Organ Procurement and Transplantation Network—Transplant Data: 1988-1997. UNOS, Richmond, VA, and the Division of Transplantation, Bureau of Health Resources and Services Administration, US Department of Health and Human Services, Rockville, MD, Table 22, 1998.
3. 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 immunoglobulin. Hepatology 1998;28:585-589.
4. Lai C, Chien R, Leung NWY, Chang TT, Guan R, Tai DI, et al. A one year trial of lamivudine for chronic hepatitis B. N Engl J Med 1998;339;61-68.
5. Villeneuve J, Condreay LD, Willems B, Pomier-Layrargues G, Fenyves D, Bilodeau M, et al. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. Hepatology 2000;31:207-210.
6. Yao Fy, Bass NM. Lamivudine treatment in patients with severely decompensated cirrhosis due to replicating hepatitis B infection. J Hepatol 2000;33:301-307.
7. Kapoor D, Guptan RC, Wakil S, Kazim SN, Kaul R, Agarwal SR, et al. Beneficial effects of lamivudine in hepatitis B virus related decompensated cirrhosis. J Hepatol 2000;33:308-312.
8. Yao FY, Terrault NA, Freise C, Maslow L, Bass NM. Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating hepatitis B infection awaiting liver transplantation: A comparative study using a matched, untreated cohort. Hepatology 2001;34:411-416.
9. Chayama K, Suzuki Y, Kobayashi M, Kobayashi M, Tsubota A, Hashimoto M, et al. Emergence and take over of YMDD motif mutant hepatitis B virus during long-term lamivudine therapy and re-takeover by wild type after cessation of therapy. Hepatology 1998;2:1711-1717.
10. Melagari M, Scaglioni PP, Wands JR. Hepatitis B virus mutants associated with 3TC and famciclovir administration are replication defective. Hepatology 1998;27:628-633.
11. Mutimer D, Pillay D, Shields P, Cane P, Ratcliffe D, Martin B, et al. Outcome of lamivudine resistant hepatitis virus infection in the liver transplant recipient. Gut 2000;46:107-113.
12. Saab S, Kim M, Wright TL, Han SH, Martin P, Busuttil RW. Successful orthotopic liver transplantation for lamivudine-associated YMDD mutant hepatitis B virus. Gastroenterology 2000; 119:1382-1384.
13. Teo EK, Han SH, Terrault N, Luketic V, Jensen D, Keeffe EB, Lok ASF. Liver transplantation in patients with hepatitis B virus infection: Outcome in Asians versus whites. Hepatology 2001; 33:126-132.
14. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-470.
15. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter-Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864-871.
16. Fontana RJ, Perrillo R, Hann HW, Wright T, Rakela J, Bacon B, et al. Determinants of survival in 133 patients with decompensated chronic hepatitis B treated with lamivudine [abstract]. Hepatology 2000;32;239A.
17. Perrillo RP, Wright T, Rakela J, Levy G, Schiff E, Gish R, et al. A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. Hepatology 2001;33:424-432.
18. Perrillo RP, Schiff ER, Yoshida E, Statler A, Hirsch K, Wright T, et al. Adefovir dipivoxil for the treatment of lamivudine-resistant hepatitis B mutants. Hepatology 2000;32:129-134.