Clinical Improvement in Patients With Decompensated Liver Disease Caused by Hepatitis B After Treatment With Lamivudine

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Lamivudine is effective in inhibiting hepatitis B virus (HBV) replication, and its clinical use in patients with chronic hepatitis B is associated with improvements in serum aminotransferase levels and liver histopathologic characteristics. Few data are available on its use in patients with advanced liver disease. We report on the outcomes of 5 patients with hepatic decompensation caused by chronic hepatitis B treated long term with lamivudine. All patients were adult white men seropositive for hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) before therapy. All 5 patients had biopsy-proven cirrhosis with clinical and biochemical evidence of hepatic decompensation. Two patients had Child's class C cirrhosis; 2 patients, class B; and 1 patient, class A (although this patient had persistent portasystemic encephalopathy and developed variceal bleeding). HBV DNA became undetectable in all patients and remained so throughout the study. Both patients with Child's class C and 1 patient with class B cirrhosis had significant clinical improvement. Child-Pugh scores improved from 12 to 7 and 11 to 7 in the 2 patients with Child's class C cirrhosis, and the patient with class B cirrhosis had complete resolution of troublesome encephalopathy. Serum aminotransferase, albumin, and total bilirubin levels improved significantly in 3 of 5 patients. One patient with Child's class B cirrhosis underwent orthotopic liver transplantation at week 13 after dramatic increases in liver tests and clinical worsening. The patient subsequently cleared HBeAg and HBsAg from serum posttransplantation. In conclusion, prolonged therapy with lamivudine resulted in improved serum biochemical values and loss of HBV DNA in patients with decompensated cirrhosis. Clinical improvements, reflected in Child-Pugh classification and functional status, may also occur, particularly among those with Child's class C disease initially. (*Liver Transpl 2000;6:715-720.*)

Chronic infection with hepatitis B virus (HBV) is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma, affecting more than 350 million people. It is responsible for approximately 1 million deaths yearly worldwide.[1] A reported 1.25 million people in the United States are infected with HBV, and 20% to 25% of these individuals have no documented risk factors.[2] The World Health Organization estimates that nearly 400 million people will be carriers of HBV by the year 2000. Until vaccination and immunization are universally accepted throughout the world, this trend can only get worse.

Interferon-α has been the mainstay of therapy for chronic hepatitis B. Published clinical data on interferon for treatment of chronic HBV suggests nearly a 33% response, gauged by hepatitis B e antigen (HBeAg) clearance.[3] Most of these data are reflective of patients with compensated liver disease compared with those with advanced stages and decompensation, who appear to have unfavorable responses and severe complications. HBV–related end-stage liver disease remains a controversial indication for transplantation because of the high incidence of posttransplantation recurrence, estimated at 60% to 90% of all cases, and inferior survival rates compared with other forms of chronic liver failure.[4]

Trials using interferon have been discouraging in patients with advanced disease, and the success seen with long-term perioperative and postoperative hyperimmune B immunoglobulin (HBIG) has met with high costs and limited supplies.[5-7] Lamivudine, an (–) enantiomer of 3-thiacytidine with potent antiviral inhibitory effects against HBV,[8] markedly reduced serum HBV DNA levels and improved biochemical and histological parameters in patients with chronic HBV infection.[8,9] However, few data exist evaluating long-term lamivudine therapy in patients with decompensated liver disease caused by HBV for the effect on serum markers of HBV replication, liver function, and the safety profile.

Recently, a series of 35 patients with decompensated cirrhosis caused by HBV were treated with lamivudine, and long-term biochemical and clinical outcomes were evaluated.[10] Here, we report and compare our findings on the biochemical and clinical outcomes of a small number of patients with decompensated cirrhosis treated with lamivudine.

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Patients and Methods

Five subjects with a clinical diagnosis of chronic hepatitis B, documented positive test results for hepatitis B surface antigen (HBsAg) and HBeAg, and evidence of hepatic decompensation were screened and enrolled onto the study. Exclusion criteria were acute fulminant hepatitis, significant clinical pancreatitis, need for ventilatory support, current use of lamivudine for HIV-related diseases, HIV seropositivity, and seropositivity for antibodies to hepatitis C virus and hepatitis D virus. None of the subjects were previously or concurrently treated with alternative antiviral regimens at the time of entry onto the study. A detailed medical history, hepatitis history, review of systems, and physical examination were performed at baseline and at regular intervals during follow-up. These 5 patients were treated at Saint Louis University (St Louis, MO) as part of a national compassionate use program sponsored by Glaxo-Wellcome (Durham, NC) aimed at patients who did not fit into the usual trials, including those with decompensated cirrhosis, liver transplantation candidates, and patients with recurrent HBV infection after liver transplantation. Data analysis was performed at Saint Louis University.

Each subject was treated with lamivudine, 100 mg/d, for an indefinite period. Clinical assessment and serological analysis were performed at regular intervals. Clinical assessment included degree of ascites and presence of encephalopathy and gastrointestinal bleeding, and patients were scored and classified according to the modifications described by Pugh et al.[11] Hematologic and serum chemistry profiles were performed at a central clinical laboratory weeks 0, 2, and 4; months 2, 3, and 4; and every 2 months thereafter. Virologic response was assessed by HBsAg, antibody to HBsAg (anti-HBs), HBeAg, and antibody to HBeAg (anti-HBe; Abbott Laboratories, North Chicago, IL), performed at baseline and every 4 months thereafter. Additionally, serial tests of serum HBV DNA (Chiron branched DNA assay; Chiron Laboratories, Emoryville, CA) were performed at baseline and every 2 months to assess appropriateness for continued therapy and development of antiviral resistance. Child-Pugh scores were tabulated at baseline and every 12 to 14 weeks.

All subjects had a previous liver biopsy performed within 6 months of beginning therapy to assess the severity of HBV-associated hepatitis and cirrhosis and help rule out other associated causes of liver dysfunction. Histological analysis was performed by a single pathologist at Saint Louis University, and all 5 subjects had biopsy-proven cirrhosis before enrollment.

Results

We studied 5 patients, all white men ranging in age from 46 to 71 years (mean, 61.4 years) with hepatic decompensation caused by chronic HBV infection who were treated with lamivudine, 100 mg/d, for 36 to 77 weeks. The biochemical, serological, and clinical course of each patient is shown in Figure 1. Brief summaries of each patient's progress to date are given.

Patient 1

This 65-year-old patient initially presented with asterixis and hypoalbuminemia, serum albumin level of 3.0 g/dL, and Child-Pugh score of 7. During the first few weeks of therapy, he had severe encephalopathy requiring hospitalization 3 times over the course of 10 to 12 weeks. Once started on lamivudine therapy, serum HBV DNA became undetectable during the study period. By week 24, serum alanine aminotransferase (ALT) values normalized, and at 48 weeks of treatment, albumin level increased to 3.3 g/dL and total bilirubin level decreased from 1.6 to 1.2 mg/dL. This patient had 2 episodes of variceal bleeding during the 48 weeks of treatment; however, his troublesome portasystemic encephalopathy (PSE) virtually resolved on therapy. Thus, he was noted to have asterixis on only 1 occasion subsequently and did not require hospitalization for this complication again.

Patient 2

This 67-year-old patient initially had mild to moderate ascites, prothrombin time of 16.9 seconds, albumin level of 2.0 g/dL, and total serum bilirubin level of 3.5 mg/dL, classifying him as Child's class C. Before therapy with lamivudine, he was seropositive for HBsAg, HBeAg, and anti-HBe. Serum HBV DNA was undetectable at baseline and remained so during the treatment period. Two weeks into treatment, this patient had a gastrointestinal bleed believed to be secondary to portal hypertensive gastropathy after esophagogastroduodenoscopy. On therapy, total bilirubin level decreased to 2.0 mg/dL, albumin level increased to 2.7 g/dL, and by week 28, the patient became anti-HBe

Figure 1. Patient 1, resolution of PSE, increase in albumin level to 3.3 g/dL, normalization of ALT level, and decrease in total bilirubin (T Bili) level to 1.2 mg/dL at 48 weeks. Patient 2, resolution of gastrointestinal bleeding, less frequent PSE, increase in albumin level to 2.7 g/dL, decrease in ALT level, and decrease in T Bili level to 2.0 mg/dL at 73 weeks. Patient 3, no adverse clinical events, increase in albumin level to 3.4 g/dL, normalization of ALT level, and decrease in T Bili level to 2.6 mg/dL at 77 weeks. Patient 4, rapid decompensation by week 13, subsequent liver transplantation, anti-HBs positive and HBsAg, HBeAg, and HBV DNA negative posttransplantation. Patient 5, resolution of variceal bleeding, less frequent PSE, and no significant change biochemically. All HBV DNA values were estimated by Chiron branched DNA assay and expressed as milliequivalents per milliliter (lower limit of detection, 0.7 mEq/mL).

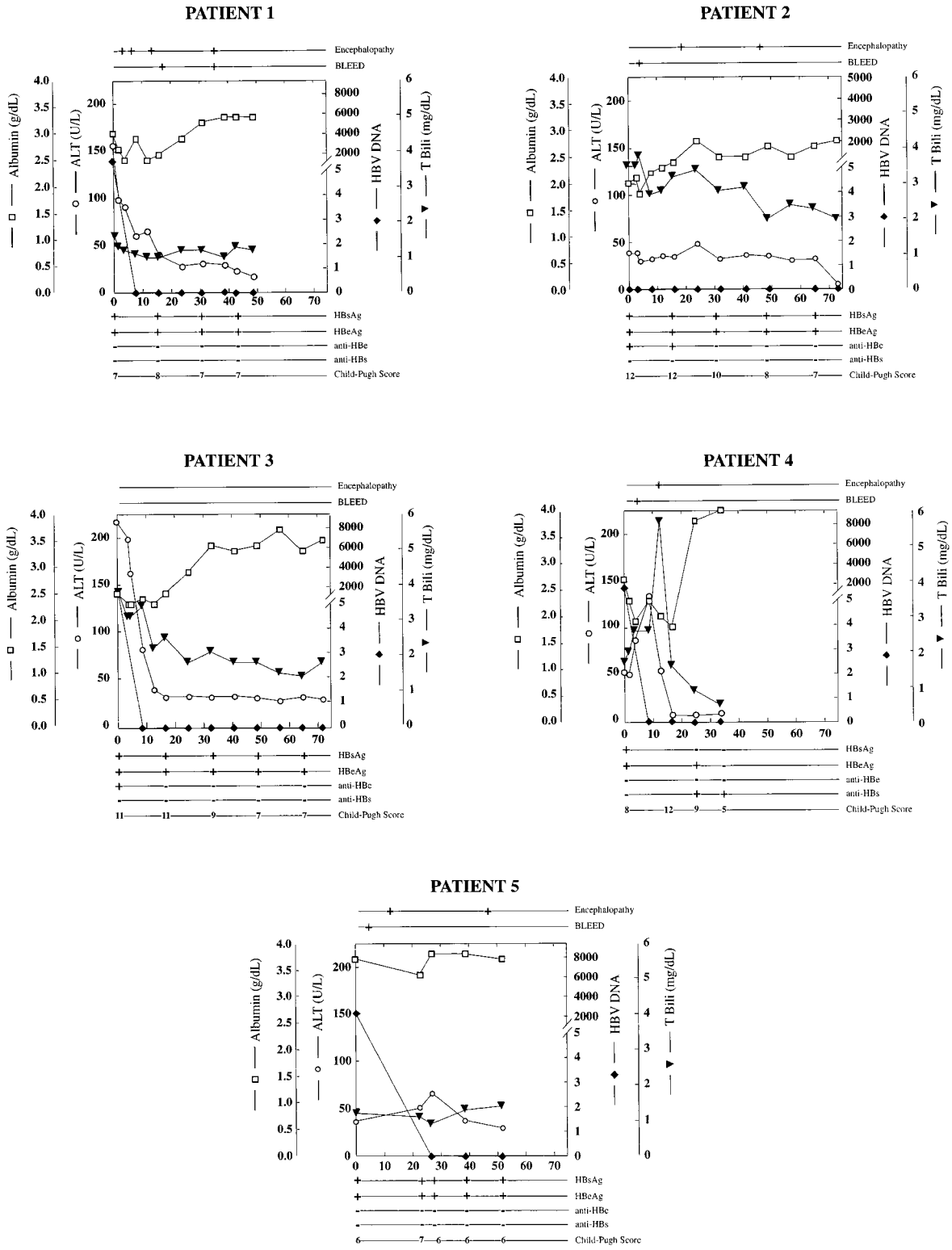
PATIENT 1
PATIENT 2
PATIENT 3
PATIENT 4
PATIENT 5
Encephalopathy
BLEED
Albumin (g/dL)
ALT (U/L)
HBV DNA
T Bili (mg/dL)
HBsAg
HBeAg
anti-HBe
anti-HBs
Child-Pugh Score

Figure 1.

negative. Although the coagulopathy did not improve, there were no further episodes of gastrointestinal bleeding. The patient continued to have a stable clinical course with only occasional occurrences of PSE and improved his Child-Pugh score from 12 to 7 at week 23 after initiating lamivudine therapy.

Patient 3

Patient 3 is a 71-year-old man who had a Child-Pugh score of 11 before therapy with lamivudine. He had an albumin level of 2.5 g/dL, prothrombin time of 14.9 seconds, and total serum bilirubin level of 3.8 mg/dL. HBV DNA became undetectable at 8 weeks and remained undetectable throughout treatment. ALT levels normalized by week 12, and by 77 weeks, total bilirubin level decreased to 2.6 mg/dL and serum albumin level increased to 3.4 g/dL. No adverse clinical events occurred throughout this period. His Child-Pugh classification improved to Childs's class B, with a Child-Pugh score of 7.

Patient 4

This 63-year-old man had mild to moderate ascites and a serum albumin level of 2.7 g/dL, classifying him as Child's class B, with a Child-Pugh score of 8 before entry onto the study. Although HBV DNA was negative within 8 weeks of treatment, by the 13th week of therapy, his ALT level increased from 52 to 133 U/L and serum bilirubin level increased from 1.7 to 2.6 mg/dL. An episode of variceal bleeding occurred during week 8, accompanied by persistent PSE. His hepatic synthetic function decreased dramatically as the albumin level decreased to 1.7 g/dL and prothrombin time increased from 11.0 to 19.4 seconds. He underwent orthotopic liver transplantation at week 13 of therapy and subsequently cleared HBsAg and HBeAg from serum. The patient remained on lamivudine therapy posttransplantation and currently remains HBsAg and HBeAg negative, with undetectable HBV DNA in serum.

Patient 5

This 46-year-old man had a single episode of variceal bleeding and persistent hepatic encephalopathy. His initial viral load was significantly elevated; however, by week 26, serum HBV DNA became undetectable. His biochemical parameters changed very little during therapy with lamivudine, maintaining Child's class A. This patient had no further variceal bleeding after initiation of therapy and decreasing episodes of PSE to 52 weeks of treatment.

In summary, 3 patients improved clinically. One patient had resolution of PSE, and 2 patients had resolution of variceal bleeding and less frequent PSE during the treatment period. Of the remaining 2 patients, 1 patient continued to be clinically stable and the other patient decompensated significantly, requiring transplantation. Biochemically, 3 of 5 patients (60%) had significant elevations in serum albumin levels and decreases in total bilirubin levels during therapy. All 5 subjects were HBsAg and HBeAg positive at the beginning of treatment and remained positive throughout therapy, except for patient 4, who became HBeAg and HBsAg negative and anti-HBs positive posttransplantation. Patients 1, 3, 4, and 5 were anti-HBe negative before therapy with lamivudine and remained negative throughout treatment. Patient 2 was initially anti-HBe positive but became negative by week 28. Collectively, 5 of 5 patients became HBV DNA negative on therapy. With respect to the development of lamivudine resistance, none of the 5 patients developed the YMDD variant phenotype. Thus, no patient had the reappearance of HBV DNA in serum after initial clearance, and all remained with persistently undetectable levels of HBV DNA to the time of this report.

Discussion

Long-term lamivudine therapy has an excellent safety profile and effectively reduces serum HBV DNA levels, necroinflammatory activity, and progression of fibrosis in patients with compensated chronic HBV infection. However, data evaluating the safety profile, biochemical parameters, and pretransplantation suppression of HBV replication with prolonged treatment of lamivudine are limited in patients with decompensated liver disease caused by HBV infection.

We found that the use of lamivudine in decompensated cirrhosis caused by HBV effectively and safely suppressed viral replication and resulted in significantly improved liver function or slowed progression of hepatic decompensation, with improvement in clinical outcome. This suggests the possibility of delaying the time to transplantation or even avoiding transplantation altogether. Lamivudine therapy may be useful in patients for whom liver transplantation is not an option, such as those with severe concurrent illnesses, or perhaps in the elderly (3 of our 5 patients were aged >65 years).

Several investigational studies used lamivudine in the setting of decompensated liver disease. Grellier et al[12] treated a series of patients with decompensated liver disease with 100 mg of lamivudine before transplant-

ation, resulting in HBsAg and HBV DNA clearance in 90% of the patients at 1 year. Bain et al[13] reported on 5 patients treated with 100 mg of lamivudine for 1 to 8 weeks before transplantation. All patients were HBV DNA negative within 1 to 2 weeks of treatment and remained HBeAg and HBsAg positive before transplantation. Only 1 patient had some improvement in aspartate aminotransferase level before transplantation, and 1 patient died after 1 week of therapy of advanced hepatocellular carcinoma. In our preliminary study, all 5 patients became HBV DNA negative and remained HBsAg and HBeAg positive while on treatment, except for patient 4, who cleared both antigens posttransplantation. Van Thiel et al[14] treated 9 patients with advanced liver disease from HBV. Four of the 9 patients went on to transplantation. Biochemical improvement was noted by ALT level normalizing in only 3 of 5 patients who did not undergo transplantation. Only 1 of 5 patients who did not undergo transplantation had an elevated serum bilirubin level (1.6 mg/dL) at entry.

Our patients included 2 patients with Child's class C cirrhosis, 2 patients with Child's class B, and only 1 patient with Child's class A. Four of 5 patients had elevated bilirubin levels (1.6 to 3.8 mg/dL), and at last follow-up, 3 of 5 patients (60%) had normal ALT levels and significantly improved total bilirubin values. Importantly, 2 of 5 patients (40%), both with Child's class C cirrhosis, clinically improved by a full Child's class at last follow-up. Patient 2 had no further gastrointestinal bleeding, resolved ascites, and improved albumin and bilirubin levels. Patient 3 had significant improvements in bilirubin and albumin values and no clinical events related to hepatic decompensation.

In a recent study, 13 potential candidates for OLT were treated with lamivudine and reported 42% normalization of ALT levels (no hepatitis C virus coinfection). Eight patients went on to transplantation, whereas 3 patients improved to allow medical and/or surgical management.[15] Time to transplantation was not reported. Markowitz et al[16] evaluated the efficacy of a prophylactic combination of lamivudine and HBIG for HBV recurrence in 14 subjects posttransplantation. All 4 patients positive for HBV DNA before transplantation were negative a median of 28 days after the initiation of 150 mg/d of lamivudine, and 1 patient became HBsAg negative before transplantation. Posttransplantation, 13 of 14 patients had undetectable HBV DNA levels at a median of 346 days on the lamivudine-HBIG combination.

In a study by Perrillo et al,[17] lamivudine was evaluated as a potential therapy for HBV posttransplantation. All 52 patients were HBV DNA positive before therapy with 100 mg/d of lamivudine, and 45 patients were positive for serum HBeAg. After 52 weeks of treatment, 60% cleared HBV DNA from serum, 31% lost HBeAg, 71% had normalized ALT levels, and 27% had detectable YMDD motif variants. Histologically, significant reductions in periportal necrosis, lobular necrosis, and portal inflammation were described.

Our experience is consistent with the results of a larger trial recently reported by Villeneuve et al.[10] Thirty-five patients with severe HBV cirrhosis were treated with 100 or 150 mg/d of lamivudine. All patients cleared HBV DNA from serum after 6 months of treatment, except for 3 patients who acquired a YMDD motif mutation of the HBV DNA polymerase. Biochemical and clinical improvement occurred in the majority of patients after 9 months of therapy. The 8 patients with Child's class B improved clinically, and 14 of 15 patients with Child's class C disease improved to either class B or class A. In our pilot study, both patients with Child's class C disease reduced their Child-Pugh scores on therapy to be designated Child's class B. One of 2 patients with Child's class B and the only patient with Child's class A disease showed significant clinical improvement on lamivudine therapy. Again, no phenotypic evidence of lamivudine resistance was noted in any subject.

We do not have an explanation for the flare of hepatitis observed in patient 4, although this type of exacerbation is well described in patients treated with interferon and may also occur (although less likely and usually milder) in patients with compensated liver disease administered lamivudine.

An important issue in the use of lamivudine in patients with decompensated cirrhosis caused by HBV is the best timing relative to transplantation. Thus, the longer the period of therapy beyond 6 to 9 months, the greater the risk for the development of lamivudine resistance. A preliminary report suggested that patients developing lamivudine resistance during or after liver transplantation have a poor prognosis.[18] However, the natural history of this clinical entity is not clear, particularly with the potential for using other antiviral agents, such as adefovir or entecavir, to treat lamivudine-resistant HBV infection.

In summary, our data show that 3 of 5 patients (60%) with decompensated cirrhosis caused by HBV had significant clinical improvement after prolonged therapy with lamivudine, characterized by a reduction in Child-Pugh score and stabilization of encephalopathy and ascites. Thus, lamivudine treatment in patients with hepatic decompensation caused by hepatitis B may prolong pretransplantation survival and delay the time

to transplantation, particularly in patients with Child's class C disease.

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