Original Article

MANAGEMENT OF DECOMPENSATED CIRRHOSIS DUE TO HbeAg-NEGATIVE CHRONIC HBV INFECTION WITH LAMIVUDINE MONOTHERAPY

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ABSTRACT

OBJECTIVE: To evaluate the efficacy of long-term lamivudine monotherapy in patients with decompensated cirrhosis due to HbeAg-negative/HBV-DNA positive.
DESIGN: Case - control study.
SETTING: Departments of Medicine and Surgery, Liaquat University Hospital, Jamshoro, and Isra University Hospital Hyderabad, from March 2000 to June 2003.
PATIENTS AND METHODS: We analyzed the clinical course and outcome of lamivudine treatment in 30 consecutive cirrhotics and compared with 30 HBV untreated HbeAg-negative controls.
RESULTS: Significant clinical improvement, defined as a reduction of at least two points in Child-Pugh score was observed in 23 of the 30 treated patients (76.6%) versus none of the 30 patients in the control group ($p< 0.0001$) after a mean follow-up of 10.6 ± 2.1 (±SD) months. There were 10 deaths in the treated group versus 24 in the control group ($p= 0.07$). Patients with clinical improvement had better survival than patients with no improvement ($p=0.04$).
CONCLUSION: Lamivudine monotherapy significantly improves liver function in HbeAg-negative decompensated cirrhosis.

KEY WORDS: *Hepatitis B Virus. Cirrhosis. Liver.*

INTRODUCTION

Hepatitis B viral (HBV) infection have been prevalent with endemicity throughout the world including Pakistan[1]. It affects more than 350 million people worldwide, or approximately 5 percent of the world's population.[2] The course of the disease varies from spontaneous viral clearance to prolonged latency, or progressive damage to the liver[3,4]. Patients with decompensated cirrhosis due to chronic hepatitis B virus infection have a poor prognosis[5], and liver transplantation appears to be the only therapeutic option for these patients at present[6]. Lamivudine, a potent nucleoside analogue, is currently approved for the treatment of patients with chronic hepatitis B. Lamivudine is highly effective in a broad range of patients and has an excellent safety profile. Current evidence suggests that a 12-month course of lamivudine achieves normal transaminase levels and no dectectable HBV-DNA by a hybridization assay in 65% of patients with compensated HbeAg-negative/ HBV-DNA-positive liver disease.[7]
In decompensated liver disease, lamivudine is associated with improvement of liver function[8-10]. However, the high rates of biochemical and virological relapses soon after discontinuation of treatment and the emergence of drug-resistant hepatitis B mutants are the two major problems with lamivudine treatment[11]. In Pakistan no information is yet available or is still under investigation, about the efficacy of prolonged lamivudine monotherapy in patients with decompensated cirrhosis due to HbeAg-negative/ HBV-DNA positive[6].
In this study, we aimed to evalute in patients with decompensated HbeAg-negative cirrhosis, the efficacy and safety of prolonged lamivudine treatment.

PATIENTS AND METHODS

The present study was carried out from March 2000 to June 2003 at the departments of Medicine and Surgery, Liaquat University Hospital Jamshoro and Isra University Hospital Hyderabad. Thirty consecutive adult patients with decompensated liver disease due to chronic HBV infection were included in this study and treated orally with lamivudine 100 mg once daily.

Decompensated liver disease was defined as Child-Pugh-Turcotte (CPT) score > 7 at screening[12].
Serum transaminase, albumin, bilirubin, amylase, and prothrombin time were measured by standarad laboratory procedures. HbsAg, HbeAg, anti-Hbe, anti-HBs, anti-HBc, anti-HCV, anti-D, and anti-HIV were measured by enzyme immunoassay. Quantification of HBV DNA was carried out using a commercially available quantitative PCR assay (AMPLICOR HBV MONITOR Assay, Roche Diagnostic Systems. NJ, USA). The stage of hepatic encephalopathy used in the CPT scoring system was based on the classification by Gitlin[13]. All the patients were followed up monthly, or when necessary. The CPT score was calculated at baseline and every 3 months, biochemistry was assessed every 2 or 3 months, alpha-fetoprotien and abdominal ultrasonography every 4 to 6 months, and serum HBV DNA was measured every 6 months. Subjects were followed until death or last visit. Virological breakthrough (VBR) was defined when serum HBV DNA rose to >100,000 copies/ml after falling below this level on lamivudine therapy. Biochemical breakthrough (BBR) was defined with the reappearance of abnormal transaminase activity after a decline to normal levels during treatment in patients with VBR. Significant clinical improvement was defined as a reduction in CPT score of atleast two points[14]. Survival was compared with that of a control group of 30 patients with decompensated chronic hepatitis B infection. The patients in the control group were selected from the cirrhotics attending or hospitalized between 2000 and 2003. They were matched for age, gender and HbeAg/anti-Hbe status with the lamivudine-treated group. Start of follow-up was considered to be the first visit or hospital admission. The follow-up ended at the time of death, or at last visit.

RESULTS

The baseline characterstics of the treated and control groups are shown in **Table I**. The two groups were not significantly different in baseline clinical or laboratory characterstics and CPT score. There were 24 males and 6 females in both groups with a mean age of 63.1 ± 1.7 years in the treated group and 62.8 ± 1.4 years in the control group. Three patients in the treated group and four in the control group had liver biopsies and all had cirrhosis. In other patients diagnosis was supported by clinical, laboratory and imaging data. Lamivudine was well tolerated by all treated patients during the treatment period and none discontinued treatment due to side effects.

TABLE I:
BASELINE CHARACTERISTICS OF THE PATIENTS AND THE CONTROLS

Characteristic	Lamivudine treated group	Control group
Age (year)	65 (43-75)	62.5 (45-80)
Gender (male/female)	24/6	24/6
HbeAg {-}/Anti-Hbe {+} (patients)	0/30	0/30
Ascites (patients)	27 (90%)	25 (83.3%)
Encephalopathy (patients)	5 (16.6%)	4 (13.3%)
History of variceal bleeding (patients)	5 (16.6%)	6 (20%)
AST (IU/L)	92.5 (43-235)	88.5(50-265)
ALT (IU/L)	77 (26-280)	80 (30-199)
PT prolongation (s)	4 (1-9)	4.5 (3-10)
Albumin (g/dl)	2.95 (2-4)	3 (2-4.7)
Bilirubin (mg/dl)	2.02 (1-6.05)	2 (1.4-13.5)
HBV DNA (copies/ml)	$3.7X10^5$ ($7.1X10^3$-$4.8X10^7$)	
Child-Pugh score	9 (8-12)	9 (9-13)
Follow-up (months)	12	12

There was a significant reduction in CPT score associated with lamivudine treatment. The mean score was 9.5 ± 1.6 at baseline, 8.3 ± 1.8 at 3 months, 6.88 ± 2 at 6 months and 6.3 ± 2.2 at 12 months of treatment ($p < 0.0001$). A similar decline in CPT score was not observed in the control group. The mean score was 9.53 ± 1.6 at baseline, 9.95 ± 1.4 and 10.6 ± 1.67 at 6 and 12 months. Significant clinical improvement was observed in 23 of 30 patients on lamivudine (76.6%) versus none of the 30 patients in the control group ($p<0.0001$). During follow-up, 18 of 30 patients (60%) entered Child-Pugh-Turcotte grade A (CPT score ≤ 7).
Additionally, values of bilirubin, albumin and prothrombin time showed improvement (not significant) during treatment **(Table II)**.

TABLE II:
BIOCHEMICAL CHANGES BEFORE AND AFTER TREATMENT WITH LAMIVUDINE

Biochemical	Baseline (30 patients)	12 months (21 patients)
Serum albumin (g/dl)	2.5 ± 0.5	3.4 ± 0.3
PT prolongation	1.9 ± 1.1	2.6 ± 4.5
Bilirubin (mg/dl)	4.5 ± 2	4.5 ± 4

There was a significant reduction of transaminase levels during treatment with lamivudine. A decline of transaminase levels within the normal range was observed in 72.4% patients (21/29) at 6 months and 79% patients (19/24) at 12 months. None of the patients lost HbsAg or changed HbeAg status. Serum HBV DNA was undetectable in 16 of 19 (84.2%), in 18 of 23(78.2%) and in 4 of 9(44.4%) patients at 6, 9 and 12 months of therapy. We examined the morbidity profile during the first 9 months of lamivudine monotherapy in 21 patients who were alive during the above period and had significant clinical improvement. None of these 21 patients developed SBP or had variceal bleeding 9 months after continuous lamivudine and 19 of them reported a reduction /discontinuation of diuretics. VBRs developed in 10 of the 23 (43.5%) patients, with an initial virological response at a median of 12 (range 8-15) months after initiation of treatment. VBRs were persistent in all patients. Of the 10 patients with VBR, 8 experienced BBR at a median of 2 (range 0-6) months after onset of VBR. BBR was persistent in all cases with a fluctuating pattern of transaminase levels. Five of 8 patients with BBR developed clinical signs of decompensation and eventually died at a median of 1 (range 1-3) month after development of BBR. The remaining 3 were stable after a median follow-up of 6 (range 0-12) months. Ten patients died at a median time of 10.5 months after initiation of treatment. Three patients died within 6 months of treatment without any significant liver function improvement. All had child-pugh grade C liver disease and serum HBV DNA > 10^5 copies/ml (median 450,000) at baseline. The remaining seven patients died after an initial significant improvement in CPT score. Twenty-four patients from the control group died after a mean follow-up of 10.6 ± 2.1 (range, 2-15) months. The number of treated patients who died at the six and nine months of treatment was significantly lower compared with that of untreated controls (5/30 vs 12/30, p=0.04). The survival rate for the 30 untreated patients who acted as controls was 73% at 6 months and 16.6% at 1 year versus 80% and 60% that was observed in treated patients.

DISCUSSION

The results of this study further confirm that lamivudine monotherapy in HbeAg-negative decompensated HBV cirrhotics has a beneficial effect on liver function and reduces morbidity and mortality[8-10,15,16]. In addition, our data clearly indicate that the development of BBR has a detrimental effect on liver function and survival. The clinical significance of lamivudine-induced YMDD mutants is still under investigation[7,11,17-19]. In decompensated liver disease, several recently published studies have suggested that the beneficial effect of lamivudine treatment on liver function remained stable despite the emergence of YMDD mutants.[8-10,20] In contrast to these studies, we have shown that the development of BBR is the crucial factor defining a detrimental outcome. According to our data five of the eight patients died soon after the reappearance of viremia and BBR. The reason for this discrepancy is not clear. Thus, monitoring of HBV viremia may be used as a predicting factor of early recognition of BBR and possibly clinical deterioration[21]. In our study, we included a retrospectively selected untreated control group and demonstrated longer survival in the group treated with lamividine. It might be argued that possible sources of bias between the two groups make the comparison weak. One potential problem is that the significant recent improvements in the medical care of patients with decompensated liver disease may be the reason for the longer survival in the treated group. The broad administration of B-blockers, the use of prophylactic antibodies, and the application of banding have been associated with an overall improvement in survival of these severely ill patients. There are only two retrospective controlled studies which evaluated survival after lamivudine treatment versus untreated patients with conflicting results[21-23]. Our results are compatible with those reported by Fontana et al[23] who did not observe any difference in survival between 162 lamivudine treated and 147 untreated patients. On the other hand, Yao et al, who compared 23 (74% HbeAg-positive) severely decompensated cirrhotics with a control group observed a significant improvement in survival.[21]The retrospective nature of the studies, their different design and the variability of the patient selection may be the reasons for the discrepancy.

In conclusion, our data clearly suggest that in decompensated HbeAg-negative HBV liver cirrhosis lamivudine improves liver function and that the development of BBR is associated with clinical

deterioration and fatal outcome. Under these circumstances, the early recognition of VBR and BBR appears to be mandatory in the management and outcome of these patients.

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