Hepatitis Monthly 2004; 4(8): 165-169

ORIGINAL ARTICLE

The Efficacy of Lamivudine in Hepatitis B – related Cirrhosis

Seyed-Moayed Alavian, Ali Kabir, Hamid Reza Torabi

Department of Gastroenterology, Baghiatallah University of Medical Sciences; Tehran Hepatitis Center, Tehran, Iran

Correspondence:
Seyed-Moayed Alavian MD.
Associate professor of gastroenterology

Address:
P.O.Box 14155/4656, Tehran, Iran

Tel: +98 541 322 98 11

Fax: 0098 21 895 80 48

E mail:
manager@iranhepgroup.info

ABSTRACT

Aim: In patients with chronic hepatitis B and compensated liver disease, lamivudine reduces serum HBV-DNA to undetectable levels within 1 to 2 months of treatment. The aim of this study was to evaluate the efficacy of lamivudine in cases with hepatitis B _ related cirrhosis.

Methods: This is a quasi-experimental study on 90 patients with cirrhosis due to hepatitis B. All patients received lamivudine at a dose of 100 mg per day, given orally for 52 weeks. The effect of the drug on liver function,
viremia and clinical stage of the disease were assessed.

Results: Mean age of patients was 53.2 ± 1.43 years. After 24 weeks and 52 weeks, there were only 28.6% and 26.4% of cases with positive HBV-DNA. Child score had a significant decrease after one year treatment with lamivudine.

Conclusion: This study presents a sufficient antiviral effect of lamivudine (Biovudine) in HBV-related cirrhosis patients.

Key Words: Cirrhosis, Hepatitis B, Lamivudine

INTRODUCTION

What do you think about the prognosis of cirrhosis due to HBV infection? Treatment with interferon-alpha in these patients results in a loss of serum HBV-DNA in a significant proportion of cases, with clinical stabilization or improvement in liver function (1, 4). However, despite the use of low dose

of interferon, treatment is often associated with severe side effects such as bacterial infections and flares of the underlying cirrhosis. Therefore, interferon-alpha is forbidden in cirrhotic patients (5). Lamivudine is a nucleoside analogue that directly inhibits viral DNA replication. In patients with chronic hepatitis B and compensated liver disease, lamivudine reduces serum HBV-DNA to undetectable levels within 1 to 2 months of treatment (6-7). A 1-year treatment is associated with normalization of transaminase levels and substantial histological improvement in many patients (8). Lamivudine is well tolerated and has few adverse effects (9).

This study is of interest because of the differences between Iran and many countries in view of: 1. the most common cause of cirrhosis in Iran is HBV (10) while in western countries it is alcoholic liver disease (11) and 2. Most of Iranian patients (60-80%) are HBeAg negative while in the western countries, a majority of them are HBeAg positive.

METHODS AND PATIENTS

The study took a year commencing May 2000 as a quasi-experimental study on patients with cirrhosis due to hepatitis B referring to Tehran Hepatitis Center. All patients received lamivudine (Biovudine, Bakhtar Biochimi, Kermanshah, Iran) at a dose of 100 mg per day, given orally for 52 weeks. Supplement therapy consisted of: vitamin K, lactulose, multivitamin, and propranolol. Patients with documented cirrhosis were eligible for the study. Cirrhosis was documented histopathologically according to liver biopsy in some cases. Others were diagnosed to be cirrhotic if they had at least two of these three criteria: 1. portal vein diameter more than 12 millimeters in sonography, 2. platelet count less than 100,000 per milliliter, or 3. two of these symptoms: icterus, ascites, splenomegaly, palmar erythema, or spider angioma. Likewise, patients were also considered cirrhotic cases if they had portal hypertension (splenomegaly in physical examination or esophageal varices in endoscopy) and one of these symptoms: encephalopathy or PT > 16 seconds. Patients with concurrent HCV or HIV infections or hepatocellular carcinoma were excluded from the study. Eligible patients were positive for HBV-DNA [more than 10^3 copies in ml by Cobas Amplicor HBV monitor test (Somerville, Newjersy, USA)] and/or abnormal serum aminotransferase concentration for at least 6 months before the start of the protocol. Follow up was done by qualitative PCR test for HBV-DNA with sensitivity of 1000 copies/ ml.

All patients were assessed for safety, tolerance, and efficacy at the end of weeks 12, 24, 36 and 52. Serum HBV-DNA was measured qualitatively before treatment and at weeks 24 and 52. The checklist included age, sex, weight, complete blood count, platelet count, Prothrombine time (PT), total and direct bilirubin, AST, ALT, alkaline phosphatase, HBeAg, HBV-DNA, serum protein and albumin and child score . Complications such as ascites, pedal edema, encephalopathy, bleeding, and need for hospitalization, were assessed in every visit.

The estimated sample size of 90 patients was based on a type I error rate of =0.05, with an assumption of treatment benefit being 50% of sustained response rate, the accuracy around this rate equal to 0.11% of standard deviation of this response, using the ratio estimation formula and loss rate equal to 12%.

A serum sample was taken and HBV, HCV, and HIV seromarkers were checked for every subject. For detection of HBV infection, HBV surface antigen (HBsAg) was determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Hepanostika HBsAg Uni-Form II microelisa system, Organon Teknika, Holland). HBeAg was determined (ETI-EBK-2, DiaSorin, Italy) as well. For HCV infection, anti-HCV antibody was detected using a third-generation ELISA kit (ETI HCV K-3, DiaSorin, Spain). Complementary test was done with the recombinant immunoblot assay (RIBA-3 Chiron, New Jersey, USA) for positive results of anti-HCV Ab. Patients with both ELISA and RIBA positive reports were considered to be infected with HCV. The serum samples were tested for anti-HIV antibody using ELISA kits (Genscreen HIV, Bio Rad, France).Hepatic inflammation and fibrosis were assessed by the Knodell histologic activity index (HAI) (12).

Statistical tests such as t, chi-square, and one way ANOVA, correlation coefficients such as phi, eta and repeated measurement method were used in analysis by SPSS version 11.5 software (SPSS Inc. Chicago, Illinois, USA). Correlations with P value < 0.05 were considered statistically significant. Informed consent was obtained from each patient in writing and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

RESULTS

Mean age of the study population was 53.2±1.43 years. There were 78 (86.7%) males. Only 16 patients had a liver biopsy showing a mean grade, stage and Knodell score equal to 8.85±1.32, 5.36±0.34, and 13.44±1.21, respectively. Cirrhosis was diagnosed in other seventy-four patients clinically. Only 10 cases had a history of the previous interferon-alpha therapy. For more information, study table1, where basic characteristics of the patients are shown. WBC, hemoglobin, platelet, PT, total and direct bilirubin, serum total protein and albumin did not have significant changes during trial. Weight of the patients had no significant change during treatment, either. The significant changes of AST, ALT, and alkaline phosphatase are shown in table 2. Only two cases had positive HBeAg before treatment. In one of them HBeAg became negative at 24th week and remained negative while in the other case it was positive during trial.

All patients had positive HBV-DNA at the start of the study. After 24 weeks and 52 weeks, there were only 28.6% (P<0.001) and 26.4% (P<0.001) of cases with positive HBV-DNA, respectively. The pattern of changes in ascites and edema is listed in table 3. Other clinical symptoms and signs such as encephalopathy, bleeding from gums, nose, and rectum did not have any significant changes. However, child score had a significant decrease from 9.71±0.38 to 7.76±0.48 after one year treatment with lamivudine (P=0.009).

Twenty-two cases (24.4%) needed hospitalization during the study period. There was only one death due to severe decompensation.

Table 1- Basic characteristics of the patients

	Measure	Unit
WBC	6002±961	/ml
Hemoglobin	13.5±0.18	mg/dl
Platelet	100476±5006 /ml	/ml
PT	16.1±0.4	Sec
bilirubin (total/direct)	2.7±0.39/1.2±0.17	mg/dl
albumin	3.2±0.11	g/dl
total protein	6.9±0.2	g/dl
Weight	69.6±1.7	Kg

Table 2- Change of AST, ALT, and alkaline phosphatase

Laboratory tests	Before trial	12th week	24th week	36th week	52nd week	Sig.
Ast	89.7±7.1	72.7±9.5	57.5±4.4	46±2.7	69.2±10.1	0.001
ALT	72.3±4.6	56±6	47.2±3.6	38.8±2.2	54.7±5.8	<0.001
Alkaline phosphatase	270.5±19.8	251.2±28.9	237.9±16.1	238.2±21.2	222.9±14.2	0.015

Table 3- The pattern of changes in ascites and edema

symptoms and signs	Before trial	12th week	24th week	36th week	52nd week	Sig.
Ascites	49 (61.2%)	39 (36.2%)	20 (24.4%)	15 (21.4%)	22 (28.6%)	<0.001
Edema	32 (39.5%)	15 (18.5%)	11 (13.3%)	4 (5.7%)	14 (18.2%)	0.022

DISCUSSION

Our mortality rate (one patient) is comparable with that of other studies (5, 13). Villanueva (5) and FY (13) had five (from 29 cases) and six (from 23 cases) deaths, respectively. Undetectable HBV-DNA level is an important index for response to treatment and its success. It was 71.4% and 73.6% after 24 weeks and 52 weeks, respectively. Although it is high, there is not any significant difference between them. It shows that majority of the cases became HBV-DNA negative during the first six months. The continuation of the therapy does not have any effect on end of therapy virologic response. An important point in our study is our difference regarding HBeAg. In western countries, most patients are HBeAg positive while the majority of the cases in Iran are HBeAg negative. In Yao et al., study there were nine HBeAg positive cases in 13 hepatitis B – related cirrhotic patients, 2 of whom were transplanted and other 7 cases were treated with lamivudine for a mean period of 17.5 months (14). Hann et al., showed that 33% of their HBV-cirrhotic patients were HBeAg negative after a mean period of 12.7 months while there were 62% HBeAg positive cases at the start of their trial (15). Although there is a significant difference between Iran and some other countries in prevalence of HBeAg cases, the rate of becoming HBeAg negative by lamivudine therapy seems to be the same.

Child score is an important factor which shows the severity and prognosis of cirrhosis. In a study the one year survival of the patients with a child score ranging between 5 and 7 was 80%. It decreases to 60% and 40% for patients with child score ranging from 8 to 10 and more than 10, respectively (14). In our study, child score decreased from 9.7 to 7.7 after 12 months of treatment with lamivudine. It was 10.3 to 7.5 in the Villeneuve study after a mean period of 19 months (5). Yao et al showed 3 score decrease in child score in their cases in comparison with 1 score increase in their control group after a mean period of 17.5 months (13). Lamivudine therapy caused a significant decrease in aminotransferases level. This trend shows the decrease in necroinflammatory activity in the liver. Kapoor et al. showed a similar effect with lamivudine therapy (16).

In the present trial, total protein and albumin did not have any changes like Kapoor study (16) while in Hann study albumin had a significant increase from 2.8 to 3.2 g/L (15). PT and serum bilirubin had no significant change during this trial. It shows the efficacy of lamivudine and its prophylactic effect on the progression of cirrhosis. This study presents a sufficient antiviral effect of lamivudine (Biovudine) in HBV-related cirrhotic patients. It can cause an acceptable improvement in the liver function and therefore increase the survival rate of these cases. It is important particularly since HBV is prevalent in Iran, and it is the most common cause of cirrhosis. The therapeutic effect of lamivudine in cirrhotic patients is of interest also due to the limitation in liver transplantation and its high cost in Iran.

REFERENCES

1. Nevens F, Goubau P, Van Eyken P, Desmyter J, Desmet V, Fevery J. Treatment of decompensated viral hepatitis B-induced cirrhosis with low doses of interferon alpha. Liver 1993; 13:15-9
2. Hoofnagle JH, Di Bisceglie AM, Waggoner JG, Park Y. Interferon alfa for patients with clinically apparent cirrhosis due to chronic hepatitis B. Gastroenterology 1993;104:1116-21
3. Perrillo R, Tamburro C, Regenstein F, Balart L, Bodenheimer H, Silva M, Schiff E, Bodicky C, Miller B, Denham C. Low-dose, titratable interferon alfa in decompensated liver disease caused by chronic infection with hepatitis B virus. Gastroenterology 1995; 109:908-16
4. Marcellin P, Giuily N, Loriot MA, Durand F, Samuel D, Bettan L, Degott C, Bernuau J, Benhamou JP, Erlinger S. Prolonged interferon-alpha therapy of hepatitis B virus-related decompensated cirrhosis. J Viral Hepat 1997; 4 (Suppl 1):21-6
5. Villeneuve JP, Condreay LD, Willems B, Pomier-Layrargues G, Fenyves D, Bilodeau M, Leduc R, Peltekian K, Wong F, Margulies M, Heathcote EJ. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. Hepatology 2000; 31:207-10
6. Dienstag JL, Perrillo RP, Schiff ER, Bartholomew M, Vicary C, Rubin M. A preliminary trial of lamivudine for chronic hepatitis B infection. N Engl J Med 1995; 333:1657-61
7. Nevens F, Main J, Honkoop P, Tyrrell DL, Barber J, Sullivan MT, Fevery J, De Man RA, Thomas HC. Lamivudine therapy for chronic hepatitis B: a six-month randomized dose-ranging study. Gastroenterology 1997; 113:1258-63
8. Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, Ng KY, Wu PC, Dent JC, Barber J, Stephenson SL, Gray DF. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. N Engl J Med 1998; 339:61-8
9. van Leeuwen R, Katlama C, Kitchen V, Boucher CA, Tubiana R, McBride M, Ingrand D, WeberJ, Hill A, McDade H. Evaluation of safety and efficacy of 3TC (lamivudine) in patients with asymptomatic or mildly symptomatic human immunodeficiency virus infection: a phase I/II study. J Infect Dis 1995; 171:1166-71
10. K. Azimi K, Sarrafi M, Alavian SM. Alavi M, Golestan SH, Mikaeili J, Malekzadeh R. Causes of cirrhosis in a series of patients at a university hospital in Tehran. Govaresh 2001; 7:19-26
11. Crawford JM. The liver and the biliary tract– Robbins pathologic basis of disease. 6th ed. WB Saunders Company, Philadelphia, 1999:845-901
12. Ishak K, Baptista A, Bianchi L, Cellea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995; 22: 696-9
13. 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; 34:411-6
14. Yao FY, Bass NM. Lamivudine treatment in patients with severely decompensated cirrhosis due to replicating hepatitis B infection. J Hepatol 2000; 33:301-7
15. Hann HW, Fontana RJ, Wright T, Everson G, Baker A, Schiff ER, Riely C, Anschuetz G, Gardner SD, Brown N, Griffiths D; United States Lamivudine Compassionate Use Study Group. A United States compassionate use study of lamivudine treatment in nontransplantation candidates with decompensated hepatitis B virus-related cirrhosis. Liver Transpl 2003; 9:49-56
16. Kapoor D, Guptan RC, Wakil SM, Kazim SN, Kaul R, Agarwal SR, Raisuddin S, Hasnain SE, Sarin SK. Beneficial effects of lamivudine in hepatitis B virus-related decompensated cirrhosis. J Hepatol 2000; 33:308-12