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Long-term Efficacy of Treatment with Lamivudine in HBeAg-Negative Patients with Decompensated Cirrhosis Due to Chronic Hepatitis B

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ABSTRACT

Background

The prognosis of patients with decompensated cirrhosis due to hepatitis B is very poor. It has been shown that lamivudine can improve liver function and delay the need for liver transplantation in HBeAg-positive patients with decompensated cirrhosis. However, information regarding long-term use of lamivudine in HBeAg-negative patients with cirrhosis is limited. The primary objective of this study was to evaluate the long-term efficacy of lamivudine in HBeAg-negative/HBeAb-positive patients with decompensated cirrhosis.

Materials and Methods

54 consecutive HBeAg-negative/HBeAb-positive patients with decompensated cirrhosis were enrolled into this study. All patients were treated with 100 mg lamivudine per day. Significant clinical improvement was defined as a decrease of at least 2 points in Child-Pugh-Turcotte (CPT) score. Repeated-measure one-way analysis of variance was used to evaluate the effect of time interval of lamivudine treatment on different variables. Kaplan-Meier survival analysis and Mantel-Cox test were used to further analyze the data.

Results

The mean±SD age of patients was 50.6±13.2 years. There were 40 male and 14 female patients. The median follow-up was 29 (range: 6-64) months. CPT score, MELD score and blood chemistries changed significantly after 6 months of therapy. The favorable changes were continued up to 2 years. In spite of worsening after 3 years, within subject effects measured by repeated-measure ANOVA, were significant for patients who have received lamivudine for 4 years or more.

Conclusions

Long-term lamivudine therapy improves liver function in HBeAg-negative/HBeAb-positive patients with decompensated cirrhosis.

Keywords: Chronic hepatitis B, Decompensated cirrhosis, Lamivudine

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INTRODUCTION

Chronic infection with hepatitis B virus (HBV) is a major health problem worldwide with approximately two billion people infected. Three-hundred and sixty million of these people are chronic carriers of HBV, resulting in over 470,000 deaths from cirrhosis or liver cancer.(1, 2), Progression to cirrhosis accounts for an annual rate of 8%-10% in HBeAg-negative chronic hepatitis

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B. The rate is slower in HBeAg-positive cases with an annual rate of 2.5%-5%.(3, 4), The reported yearly incidence of hepatic decompensation is 3% with a 5-year cumulative incidence of 16%.(3, 5, 6, 7), Patients with decompensated cirrhosis due to chronic hepatitis B infection have a survival rate of only 14%.(8), For the time being, liver transplantation appears to be the only therapeutic option for these people. The inadequate number of transplantation centers, high cost and long waiting list make this treatment modality unfeasible for developing countries. Other therapeutic modalities that could improve liver function, prolong survival and that delay transplantation should be investigated. In decompensated liver disease lamivudine is associated with improvement of liver function. It was shown that lamivudine is effective in HBeAg-negative patients with decompensated cirrhosis. However, the significance of prolonged therapy and rate of breakthrough phenomenon need further investigation. The objective of this study was to evaluate the efficacy of prolonged treatment with lamivudine in HBeAg-negative patients with decompensated cirrhosis.

MATERIALS AND METHODS

Between January 2000 and January 2006, 55 consecutive patients with decompensated liver cirrhosis were enrolled into this study. All patients had:

1) Positive HBsAg, negative HBeAg and positive anti-HBe antibody for at least six months.
2) Decompensated cirrhosis, defined by a Child-Pugh-Turcotte (CPT) score≥7.(9)
3) Positive qualitative HBV-DNA (PCR), if quantitave HBV-DNA was not available.

Patients were excluded if had co-infection with hepatitis C (HCV) or D (HDV) viruses, hepatocellular carcinoma (HCC) or cirrhosis due to other causes. All patients had CPT score of either class B or C. Therefore, decompensated liver cirrhosis was diagnosed on clinical basis and none of them underwent liver biopsy. Ascites was detectable in all patients by clinical examination. Baseline sonography was performed primarily for identification of liver morphology and evaluation of portal hypertension. In addition, we also assessed the model for end-stage liver disease (MELD) score according to the formula provided elsewhere.(10,11), Originally, the following equation was used to compute the MELD score:(10)

3.8 ln [bilirubin (mg/dL)] +11.2 ln (INR) +9.6 ln [creatinine (mg/dL)] + 6.4

Recently, a webpage provided another formula which makes the computation much easier and gives rounded figures and consider the age also. We compared the results of both computations. Although, the figures obtained from the website were somewhat higher comparing to the figures derived from the original formula, the patterns of changes of both formulas were the same by different time interval. Because of those reasons we chose the web-based equation (11) to calculate MELD score for patients.

The participants signed an informed written consent and treated with 100 mg lamivudine/day (Bakhtar Bioshimi Co, Kermanshah, Iran). Clinical improvement was defined as a decrease in the CPT score of at least two points. Biochemical breakthrough (BBR) was defined as a reappearance of abnormal trnsaminase (ALT) activity after a decline to normal.

The following information was recorded at the baseline and every two months, thereafter. CPT score, MELD score, complete blood count (CBC), platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin (direct, indirect), alkaline phosphates, α-fetoprotein, HBV serology (HBsAg, HBsAb, HBeAg, HBeAb), and prothrombin time. Abdominal sonography was done every six months. Viral serology was done using an ELISA commercial kit (Dia-Pro; Milano; Italy). Routine biochemical tests were done by an autoanalyzer (Abbott Alcyon-300, Abbott Laboratories, IL, USA). Hematologic tests were performed using automated techniques (Sysmax

K-100, Japan). HBV DNA was isolated and the S-gene was amplified. The amplified PCR product was run on agarose gel and read as positive or negative. The sensitivity of PCR was about 500 copies/mL.

Statistical analysis

Data were analyzed by SPSS version 13 (SPSS Inc, Chicago, IL, USA). Descriptive results were reported as mean±SD and median. Independent sample Student's t test was used to compare baseline parameters of dead and alive patients. Binary regression analysis was used to calculate the effect of baseline parameter on survival. Repeated-measures one-way ANOVA was used to compare mean of the same variable in specified duration of follow-up. Survival analysis was carried out by Kaplan-Meier method and its significance was analyzed by LogRank (Mantel-Cox) test. p value <0.05 was considered statistically significant.

RESULTS

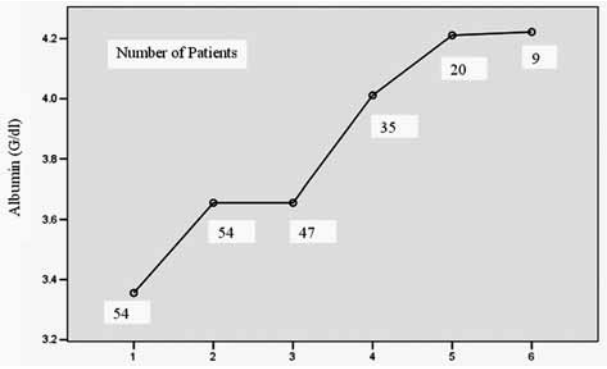
Fifty-four patients with HBV-related decompensated cirrhosis were enrolled into this study. All patients received 100 mg lamivudine/day. In addition, patients received β-blockers, lactulose, diuretics and prophylactic antibiotics according to their conditions. The mean±SD age of patients was 50.6±13.2 years. The baseline CPT score, MELD score and essential biochemical variables were measured over the follow-up; analysis was done twice for each variable (Table 1). The purpose of the first and second analysis was to show the effect of lamivudine for 24 and ≥ 48 months. In the first analysis, variables at baseline, 6, 12 and 24 months were analyzed. In the second analysis, data of 36 months, and ≥48 months were added. The minimum and maximum duration of time for treatments were six and 64 months, respectively. The mean±SD time for decrease in the (CPT) score of at least two points, was 8.6±5.3 (median: 6; range: 3-24) months. The drop in CPT score, MELD score and biochemical variables were dramatic between 6 and 12 months of follow-up. The favorable response has been continued up to 24 months. The differences observed were statistically significant and the changes followed a linear pattern. All of the

Table 1. Mean±SD of biochemical parameters, CPT score and MELD score before and after treatment with lamivudine.

Time interval (Number of patients)	ALT (IU/L)	AST (IU/L)	Bilirubine (mg/dL)	Prothrombin time (s)	Albumin (mg/dL)	Ascites	CPT score	MELD score
Baseline (n=54)	120.9±166.4	118.8±123.8	2.9±2.0	16.9±2.0	3.5±0.7	1.5±0.5	8.0±1.3	15±3
6 months (n=54)	44.03±31.9	55.5±46.8	2.0±1.1	16.4±2.2	3.8±0.6	1.2±0.4	6.5±1.6	13±4
12 months (n=47)	36.7±24.0	46.2±29.	2.4±4.6	16.1±2.2	3.8±0.5	1±0.3	6.1±1.5	12±4
24 months (n=35)	39.5±18.3	48.7±19.9	1.9±1.1	163±16.5	3.8±0.5	1±0.3	6.0±1.3	12±4
36 months (n=20)	70.9±64.7	72.6±64.7	4.2±7.8	16.9±2.2	3.9±0.9	1.1±0.4	7.0±1.9	15±5
≥48 months (n=9)	45.3±26.3	52.4±25.1	2.1±1.6	15.6±1.9	4.0±0.6	1	6.3±1.1	11±4
p-value at 24 months	=0.000 (linear)	=0.001 (linear)	=0.002 (linear)	=0.05 (linear)	=0.000 (linear)	=0.000 (linear)	=0.000 (linear)	=0.000 (linear)
p-value at ≥ 48 months	=0.1 (quadratic)	=0.04 (quadratic)	=0.007 (quadratic)	= 0.35 (linear)	=0.01 (linear)	0.056 (linear)	=0.002 (quadratic)	=0.02 (cubic)

* p-value was assessed by repeated-measure ANOVA for the tests of within-subject effects

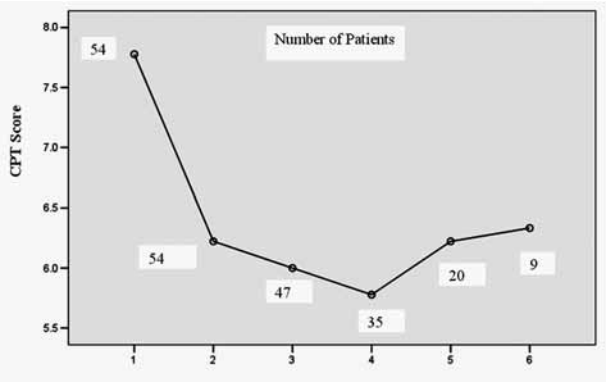
differences observed in the second analysis, for the longer interval, but those of ALT and prothrombin time, were also statistically significant, (Table1). The pattern of changes was not uniform in the second analysis; it was significant and linear for albumin (Figure1), significant and quadratic for CPT score (Figure2) and significant and cubic for MELD score (Figure 3). Overall, the best response was observed by receiving 24 months of lamivudine. Gradually, the mean value of all variables started to get worse. In spite of worsening of the mean values, the within-subject effects were statistically significant in repeated-measure ANOVA. This indicates that lamivudine



p =0.003, the pattern is linear

Time interval (months)	Baseline	6 M	12 M	24 M	36 M	≥48 M
	1	2	3	4	5	6

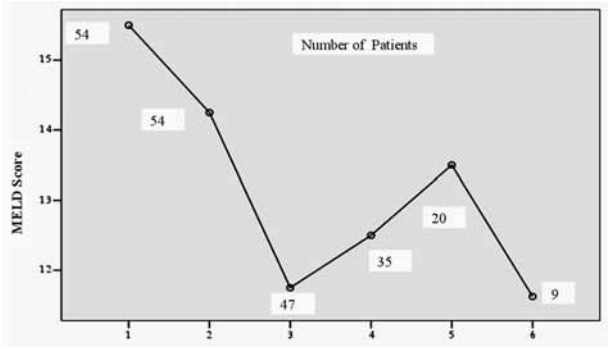
Figure 1: Serum albumin level in treated patients at different time intervals.



p =0.002, pattern is quadratic

Time intervals (months)	Baseline	6 M	12 M	24 M	36 M	≥48
	1	2	3	4	5	6

Figure 2: Changes of CPT score in treated patients at different time interval.



p =0.02, pattern is cubic

Time intervals (months)	Baseline	6 M	12 M	24 M	36 M	≥48 M
	1	2	3	4	5	6

Figure 3: Changes of MELD score in treated patients at different time intervals.

could have beneficial effects even if given for more than 24 months. The clinical responses were 60% for six months which increased to 77% for those patients who received 24 months of lamivudine (Table 2); the response rate was lower for longer intervals. Overall, the best response rate was seen in 24 months of lamivudine therapy (Table 2).

Eleven patients died of hepatic failure; none of them developed HCC. Baseline parameters such as time of treatment and follow-up, CPT score, MELD score and biochemical variables were compared and analyzed between dead and alive patients (Table 3). In binary regression analysis, none of the basal parameters could predict the

Table 2: CPT class changes and the response rate in treated patients at different time intervals.

	Baseline (n=54)	6 M (n=54)	12 M (n=48)	24 M (n=36)	36 M (n=20)	≥48 M (n=9)
A	0.00	32	33	27	12	6
CPT Class B	46	17	12	7	17	3
C	9	7	2	1	1	0.00
Response Rate (%)		60	72.3	77.1	45	33

M= Months
Response Rate=Decrease in CPT score of at least 2 points.
p<0.001, the pattern is linear up to 24 months.
p=0.002, the pattern is quadratic at ≥ 48 months.

Table 3: Mean±SD of baseline characteristics between deceased and alive patients.

Variable	Deceased (n=11)	Alive (n=43)	p-value*
AST (IU/L)	100.6±83.8	123.4±132.5	0.6
ALT (IU/L)	106.6±87.2	124.6±181.8	0.7
Creatinine (mg/dL)	0.8±0.1	0.8±0.2	0.3
Bilirubine (mg/dL)	2.9±1.2	2.9±2.2	0.9
Albumin (g/dL)	3.5±0.6	3.6±0.7	0.8
Prothrombin time (S)	16.6±2.1	17±2	0.5
Age (Yr)	47±14	51.5±13	0.3
Time interval for treatment (Months)	24±13.2	29.5±16	0.3
CPT score	8.4±1.4	8±1.2	0.3
MELD score	14.6±4	15.2±3	0.7

*p-value was was assessed by independent sample Student's t-test. The baseline values were not significantly different comparing deceased and alive patients.

outcome for death.

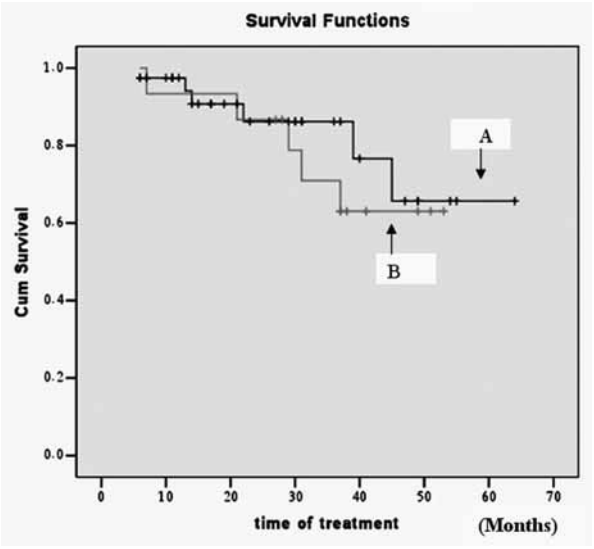
Survival curve was studied by Kaplan-Meier analysis. In this study, the 5-year cumulative survival rate was 60% after a median follow-up of 29 (range: 6-64) months. The mean±SD follow-up was 28±15.4 months. Further analysis of survival curve was performed according to the occurrence of biochemical breakthrough as a factor (Figure 4). Although the survival in patients with biochemical breakthrough was lower comparing to those without breakthrough, the difference was not significant by LogRank Mantel-Cox analysis (p=0.5).

Biochemical breakthrough was 18%, 35% and 40% after receiving 24, 36 and ≥48 months of lamivudine therapy, respectively. All patients tolerated lamivudine and no significant side effects were observed.

DISCUSSION

This study was done on HBeAg-negative, HBeAb-positive patients with decompensated liver cirrhosis. The most favorable effect was seen two years after the start of treatment. None of the patients developed HCC and the cause of death was liver failure and its complications. Baseline variables were non-significant comparing dead and alive patients in long-term follow-up.

Previous study has shown the effectiveness of lamivudine therapy in decompensated cirrhosis. In a study, Yao, *et al*, followed 23 patients, 74% of whom were HBeAg-positive, for a median of nine months.(12), In another study, by Villeneuve, *et al*, on 35 patients, 20 of whom were HBeAg-positive, only 20 patients were followed up to 19 months.(13), Tseng, *et al*, reported a total of 30 patients; nine were HBeAg-positive and only 20 received six months of lamivudine.(14), The main problem with these studies were their short-term follow-up and putting both HBeAg-positive and negative patients in the same basket.



The curve in blue (A) is the survival curve of patients without biochemical breakthrough.
The curve in green (B) is the survival curve of patients with biochemical breakthrough.
The difference was not statistically significant (p=0.5) by LogRank, Mantel-Cox analysis.

Figure 4: Cumulative 5-year survival rate of patients with HBV-related decompensated cirrhosis with lamivudine either with or without biochemical breakthrough.

There are few studies in which the effectiveness of lamivudine was studied in a pure population of HBeAg-negative patients with decompensated cirrhosis. Nikolaidis, *et al*, studied 20 patients of whom 14 received lamivudine for two years.(15), In another study by Manolakopoulos, 30 HBeAg-negative patients were enrolled but only twelve could be followed up to 24 and one case up to 36 months.(16), Problems with these studies were the small sample studied and short-term follow-up. Our study with a large number of patients and longer follow-up, further confirms that lamivudine is effective in treatment of HBeAg-negative patients with decompensated cirrhosis.

We analyzed the effect of time on lamivudine treatment by repeated-measure ANOVA. The analysis showed that the effectiveness of lamivudine was significant and the patterns of changes were linear up to two years. In addition, it was shown that lamivudine was effective for patients who had received up to four years or more. For longer than two years, the pattern of changes was no longer linear for all variables. For albumin, the overall response was significant and linear. For CPT score, the pattern was quadratic. This indicates that after two years, the CPT score increases but by continuing the treatment, CPT score drops again. The pattern for MELD score was cubic. This simply means that the shape of the curve was sinusoid and eventually, patients showed significant favorable response. In brief, the overall analysis indicated that lamivudine therapy for four years or even more had significant beneficial effects. The possible reason for this pattern of responses could be due to the effect of lamivudine resistance which can make the situation worse after two years and the presence of stable cases after three years which might have positive influence in the analysis eventually.

Recently, the MELD score has been shown to be superior to the CPT score in ranking patients according to the severity of liver disease and rank of dying. MELD score is considered to be more reproducible than CPT score because it does not include subjective variables such as encephalopathy.(10, 17), However, obtaining the score requires computation and is therefore less practical than CPT score. Moreover, the MELD score has not been proved to be superior to CPT, in terms of predictive accuracy.(15, 18, 19), Considering all these facts, CPT score is still the most widely-used index both in clinical practice and in clinical research. In this work, both CPT and MELD scores have been calculated. We found that there was no difference in predicting mortality between them. Therefore, we used CPT score as an end-point.

Lamivudine was shown to decrease significantly the incidence of hepatic decompensation and risk of HCC.(20), Improved survival was observed by Manolakopoulos in 30 patients who were treated with lamivudine, though the difference was not statistically significant (p=0.07) comparing to the control group.(16), The same pattern was shown by Fontana, *et al*, who treated 162 cases with lamivudine and 147 untreated controls.(21), On the other hand, Yao, *et al*, who compared 23 (74% HBeAg-positive) patients with severe decompensated cirrhosis with historical controls observed significant improvement in survival.(12)

Overall, the cumulative 5-year survival rate in our study was 60%. The cumulative 5-year survival curve of the patients with biochemical breakthrough was lower than those without the breakthrough, although the difference was not statistically significant. It is difficult to compare the cumulative survival rate with other reports due to different follow-up schemes. However, our results were in keeping with two other works.(12, 16), It can be argued that for lack of a control group, this study did not prove the survival benefit of lamivudine. However, the historical control that was used by other researchers has clearly shown that lamivudine increased survival comparing to untreated groups.(8, 16, 21, 22), Therefore, for ethical considerations, untreated control group was not used in this study. Biochemical breakthrough was not observed at one year. However, it occurred with a rate of 18% at two years and 35% at three years of treatment. The figures are in the same range as was reported by others.(23, 24), However, serial HBV-DNA was not measured in this work. Therefore, we could not comment on viral breakthrough which precedes the clinical breakthrough.

A major shortcoming of this work was the lack

of serial measurements of the number of copies of HBV-DNA. Therefore, we were not able to comment on the pattern of lamivudine effect on HBV-DNA, viral breakthrough, mutations and their deleterious effects on liver decompensation and mortality in this study. However, according to the most recent NIH algorithm for treatment of chronic HBV infection, all decompensated cirrhotic patients, regardless of their HBV-DNA level, should be considered for treatment. In this respect, baseline positive qualitative PCR becomes important in making decision for the treatment, if quantitative HBV-DND is not available.(25)

CONCLUSION

In conclusion, we found that lamivudine can cause significant drop in both CPT and MELD score. It caused significant improvement in liver synthetic functions and enzymes. Using lamivudine for two years associates with biochemical breakthrough. In spite of biochemical breakthrough, continuing use of lamivudine is not associated with any deleterious effects.

References

1- Kane M. Global programme for control of hepatitis B infection. *Vaccine* 1995; 13 Suppl 1: S47-9.
2- Lee WM. Hepatitis B virus infection. *N Engl J Med* 1997; 337(24): 1733-45.
3- Ikeda K, Saitoh S, Suzuki Y, Kobayashi M, Tsubota A, Koida I, *et al*. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. *J Hepatol* 1998; 28: 930-8.
4- Fattovich G, Brollo L, Giustina G, Noventa F, Pontisso P, Alberti A, *et al*. Natural history and prognostic factors for chronic hepatitis type B. *Gut* 1991; 32: 294-8.
5- Di Marco V, Lo Iacono O, Camma C, Vaccaro A, Giunta M, Martorana G, *et al*. The long-term course of chronic hepatitis B. *Hepatology* 1999; 30: 257-64.
6- Realdi G, Fattovich G, Hadziyannis S, Schalm SW, Almasio P, Sanchez-Tapias J, *et al*. Survival and prognostic factors in 366 patients with compensated cirrhosis type B: a multicenter study. The Investigators of the European Concerted Action on Viral Hepatitis (EUROHEP). *J Hepatol* 1994; 21: 656-66.
7- Fattovich G, Giustina G, Schalm SW, Hadziyannis S, Sanchez-Tapias J, Almasio P, *et al*. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. The EUROHEP Study Group on Hepatitis B Virus and Cirrhosis. *Hepatology* 1995; 21: 77-82.
8- De Jongh FE, Janssen HL, de Man RA, Hop WC, Schalm SW, van Blankenstein M. Survival and prognostic indicators in hepatitis B surface antigen-positive cirrhosis of the liver. *Gastroenterology* 1992; 103: 1630-5.
9- Child CG, Turcotte JG. Surgery and portal hypertension. *Major Probl Clin Surg* 1964; 1: 1-85.
10- 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: 464-70.
11- www.unos.org/resources/meldpeldcalculator.asp
12- Yao FY, Terrault NA, Freise C, Maslow L. 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: 411-16.
13- Villeneuve JP, 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: 207-10.
14- Tseng PL, Lu SN, Tung HD, Wang JH, Changchien CS, Lee CM. Determinants of early mortality and benefits of lamivudine therapy in patients with hepatitis B virus-related decompensated liver cirrhosis. *J Viral Hepat* 2005; 12: 386-92.
15- Nikolaidis N, Vassiliadis T, Giouleme O, Tziomalos K, Grammatikos N, Patsiaoura K, *et al*. Effect of lamivudine treatment in patients with decompensated cirrhosis due to anti-HBe positive/HBeAg-negative chronic hepatitis B. *Clin Transplant* 2005; 19: 321-6.
16- Manolakopoulos S, Karatapanis S, Elefsiniotis J, Mathou N, Vlachogiannakos J, Iliadou E, *et al*. Clinical course of lamivudine monotherapy in patients with decompensated cirrhosis due to HBeAg negative chronic HBV infection. *Am J Gastroenterol* 2004; 99: 57-63.
17- Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, *et al*. United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; 124: 91-6.
18- D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006; 44: 217-31. Epub 2005 Nov 9.
19- Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. *J Hepatol* 2005; 42 Suppl(1): S100-7. Epub 2004 Dec 24.
20- Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, *et al*. Cirrhosis Asian Lamivudine Multicentre Study Group. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; 351: 1521-31.
21- Fontana RJ, Keeffe EB, Carey W, Fried M, Reddy R, Kowdley KV, *et al*. for the National Institutes of Health Hepatitis B Virus Orthotopic Liver Transplantation Study Group. Effect of lamivudine treatment on survival of 309

North American patients awaiting liver transplantation for chronic hepatitis B. *Liver Transpl* 2002; 8: 433-9.
22- Weissberg JI, Andres LL, Smith CI, Weick S, Nichols JE, Garcia G, *et al*. Survival in chronic hepatitis B. An analysis of 379 patients. *Ann Intern Med* 1984; 101: 613-6.
23- Villeneuve JP, Condreay LD, Willems B, Pomier-Layrargues G, Fenyves D, Bilodeau M, *et al*. Lamivudine treatment for decompensated cirrhosis resulting form chronic hepatitis B. *Hepatology* 2000; 31: 207-10.
24- Perrillo RP, Wright T, Rakela J, Levy G, Schiff E, Gish R, *et al*. Lamivudine North American Transplant Group. A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. *Hepatology* 2001; 33: 424-32.
25- Keeffe EB, Dietrich DT, Han S-H B, Jacobson IM, Martin P, Schiff ER, *et al*. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: An update. *Clinical Gastroenterol and Hepatol* 2006; 4: 936-062.