

The impact of long-term potent antiviral therapy on the natural course of disease in patients with hepatitis B virus-related cirrhosis

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Abstract

Background and Aim: The present study compared the long-term efficacy of weak and potent antiviral treatments in patients with hepatitis B virus (HBV)-related cirrhosis.

Materials and Methods: A total of 120 patients with HBV-related cirrhosis were enrolled. The primary outcome measure was viral suppression. A secondary outcome measure was to determine the development of decompensation or hepatocellular carcinoma (HCC).

Results: The virological response (VR) was significantly better in patients treated with potent antiviral agents than in those treated with weaker antiviral agents over time ($p < 0.001$). With intention-to-treat, the VR after 1 year, 2 years, 3 years, and 4 years of potent antiviral treatment was 69.7%, 77.0%, 82.2%, and 81.2%, respectively, while the VR with weak antiviral therapies was 50.0%, 41.6%, 37.5%, and 37.5%. HBeAg (Hepatitis B e-Antigen) loss was achieved in 30.4% of HBeAg-positive patients. None of the patients had experienced HBsAg loss while on antiviral treatment. New HCC developed in 10 patients. The cumulative probability of the development of HCC was 2.6% at 1 year, 6.8% at 2 years, and 8.7% at 3 and 5 years of antiviral therapy. MELD scores among patients treated with potent antiviral treatment significantly improved from baseline to week 60 ($p = 0.006$). Antiviral therapies were well tolerated.

Conclusion: Potent antiviral treatment effectively maintained VR in the long-term follow-up of patients with HBV-related cirrhosis. HCC may still develop, albeit at a lower rate in these patients.

Keywords: Chronic hepatitis B; cirrhosis; entecavir; lamivudine; tenofovir disoproxil fumarate.

Introduction

Hepatitis B virus (HBV)-related chronic liver disease (CLD) and cirrhosis remain a major cause of liver disease-related morbidity and mortality in Türkiye.^[1,2] HBV-related cirrhosis with/without hepatocellular carcinoma (HCC) accounted for approximately half of cases of liver transplantation.^[1-4] Etiological trends of cirrhosis are also changing in Türkiye.

Morbidity and mortality in patients with chronic viral hepatitis are linked to the persistence of viral replication. Viral suppression with oral antiviral therapy against HBV has achieved clinical benefits due to the prevention of disease progression, reduction in hepatic decompensation, and HCC development.^[5-8] Lamivudine (LMV), adefovir dipivoxil (ADV), entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) are inhibitors of HBV polymerase/reverse transcriptase.^[7] Currently, LMV and ADV are no longer used in the treatment of chronic hepatitis B (CHB).^[7] The aims of the present study were to compare the long-term efficacy of weak antiviral therapies, such as LMV or ADV, and potent antiviral treatments, such as ETV or TDF, in patients with HBV-related cirrhosis, and to investigate whether virological response (VR) with these antiviral treatments results in a lower probability of disease progression and the development of HCC in such patients.

Materials and Methods

Patients

This was a retrospective single-center HBV cohort study. A total of 120 consecutive patients with HBV-related cirrhosis were enrolled in the study between January 2005 and January 2014. The diagnosis of CHB was made based on the biochemical, serological, virological, and histological data, when available.^[7] ICD-10 codes were used to identify CHB, cirrhosis, and its complications. Among the 120 patients, 24 were treated with LMV, 100 mg daily; 35 were treated with ETV, 0.5 mg daily; while 61 were treated with TDF, 245 mg daily, at the investigators' discretion. All cirrhotic patients were followed for at least 6 months. Decompensation of cirrhosis, including ascites, variceal bleeding (VB), hepatic encephalopathy (HE), acute kidney injury (AKI), and HCC, were evaluated. Data were collected from outpatient visit charts. The Ankara University School of Medicine Ethics Committee of our faculty approved this study (Ethics Decision Number: 01-04-14, 13.01.2014). The Declaration of Helsinki conducted our study.

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Table 1. Characteristics of patients with HBV-related cirrhosis

	Overall (n=120)	HBeAg positive (n=23)	HBeAg negative (n=97)	p
Age (year)	55.9±10.4 (57)	52.7±11.5 (54)	56.7±10.0 (58)	0.101
Gender (M/F)	96/24	18/5	78/19	0.778
Baseline ALT (U/L)	67.2±71.0 (43.5)	72.2±52.4 (48)	66.0±75.0 (40)	0.158
Baseline HBV-DNA Log 10 IU/ml	4.9±1.2 (3.45)	8.7±1.8 (2.9)	4.0±1.0 (2.9)	0.243
Baseline total bilirubin (mg/dl)	1.48±1.8 (1.18)	1.34±1.3 (1.1)	1.51±1.9 (1.2)	0.33
Baseline GGT (U/L)	75.8±96.8 (45)	35.7±15.5 (34)	85.2±105.3 (50)	0.014
Baseline albumin (g/dl)	3.75±0.57 (3.8)	3.8±0.56 (3.9)	3.74±0.57 (3.8)	0.59
Baseline INR	1.12±0.1 (1.1)	1.09±0.1 (1.08)	1.13±0.1 (1.1)	0.30
Baseline creatinine (mg/dl)	0.85±0.2 (0.82)	0.87±0.2 (0.82)	0.85±0.2 (0.82)	0.53
Thrombocyte count X 10 ⁹ /lt	146±67.3 (142)	161±63.1 (172)	142±68.1 (138)	0.23
Baseline MELD score	9.16±2.7 (8)	8.65±2.9 (8)	9.28±2.7 (9)	0.13

Data were given Mean±SD (median). SD: Standart deviation; HBeAg: Hepatitis B e-Antigen; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; GGT: Gamma-glutamyl transpeptidase; INR: International normalised ratio; MELD: Model for end-stage liver disease.

Methods

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin, and complete blood cell counts were measured by our central laboratory. Serological markers for viral infections (anti-HAV IgM, HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc IgG, anti-HCV, anti-HDV, anti-HIV, anti-HEV, anti-cytomegalovirus [CMV], anti-herpes simplex virus [HSV], and anti-Epstein-Barr virus [EBV]), serum iron, ferritin, ceruloplasmin, and alpha-1 antitrypsin levels were measured. Serological studies were performed for anti-nuclear antibodies, anti-smooth muscle antibodies, anti-liver kidney membrane-1, and anti-mitochondrial antibodies. All patients underwent abdominal sonography confirming the presence of cirrhosis, its complications, and HCC. HBV DNA levels were measured using the Roche COBAS TaqMan assay. HBsAg and HBeAg loss, seroconversion, and drug resistance were monitored.

Definitions

The primary outcome measure was VR, as defined by serum HBV DNA negativity. Intention-to-treat (ITT) analysis was used to evaluate VR under antiviral treatment. A secondary outcome measure was to determine the development of decompensation or HCC. A virological breakthrough was defined as a >1 log10 increase in serum HBV DNA level above nadir or confirmed detectability of HBV DNA after having an undetectable result.

Follow-up

Patients were seen at 3-month intervals in the outpatient clinic during the follow-up period. A physical examination and biochemical, serological, and virological tests were performed at each visit. The Model for End-Stage Liver Disease (MELD) score was used to assess the severity of chronic liver disease. Further investigations included surveillance for HCC with radiological imaging and

alpha-fetoprotein determinations every 6–12 months. If necessary, dynamic computed tomography or magnetic resonance imaging was performed. Possible adverse events (AE) of the antiviral agents were assessed.

Statistical Analyses

Data analysis was performed using Statistical Package for the Social Sciences version 22.0 (SPSS, Inc., Chicago, IL, USA). Mean, standard deviation, median, and percent were used for descriptive statistics. The conformity of the data to the normal distribution was assessed with a histogram and the Kolmogorov-Smirnov test. Comparisons were made using the Paired Samples t-test and the Independent Samples t-test, as appropriate. Nominal variables were evaluated using the Chi-Square test. Kaplan-Meier analysis was used to estimate the cumulative risk of HCC, cumulative HBeAg seroconversion, and emergence rate of LMV resistance. A p-value less than 0.05 was considered significant.

Results

A total of 120 cirrhotic patients were enrolled in the analysis. The median age was 57.0 years (range, 29–86 years), 80% were men, and 19.2% were HBeAg-positive. The median baseline serum alanine aminotransferase (ALT) and HBV DNA levels were 43.5 U/L and 3.45 log10 copies/mL, respectively. No significant differences in baseline characteristics among patients with e-antigen positive or negative were observed, except baseline serum GGT levels were higher in patients with HBeAg negative (85.2±105.3 U/L vs 35.7±15.5 U/L, p=0.014). The baseline characteristics of the patients are given in Table 1.

Among 120 cirrhotic patients, 77.5% of them were compensated, and 22.5% were decompensated: 75% of the patients were classified as having Child-Pugh class A, 21.7% as having Child-Pugh class B, and 3.3% as having Child-Pugh class C. Ascites (66.7%) was the most common finding of decompensation, followed by VB (22.2%) and AKI (11.1%). Median Child-Pugh and MELD scores were 5 (range: 5–10) and 8

Table 2. Baseline characteristics of patients treated with potent and weak antiviral agents

	Patients on Potent Antivirals (TDF/ETV)	Patients on Weak Antivirals (LMV)	p
Age (year)	54.8±9.8 (57)	60.5±11.57 (59.5)	0.015
Gender (M/F)	75/21	21/3	0.400
Baseline ALT (U/L)	72.7±76.9 (46.5)	44.7±31.4 (38.5)	0.055
Baseline HBV-DNA Log 10 IU/ml	4.94±1.2 (3.0)	4.78±1.28 (5.6)	0.995
Baseline total bilirubin (mg/dl)	1.47±1.97 (1.10)	1.51±0.89 (1.27)	0.21
Baseline GGT (U/L)	69.6±95.0 (42.5)	100.3±102.3 (65)	0.021
Baseline albumin (g/dl)	3.8±0.6 (3.9)	3.5±0.6 (3.5)	0.044
Baseline INR	1.11±0.2 (1.1)	1.15±0.2 (1.15)	0.258
Baseline creatinine (mg/dl)	0.83±0.2 (0.81)	0.93±0.2 (0.85)	0.068
Thrombocyte count X 10 ⁹ /lt	149±68 (147)	132±62 (127)	0.269
Baseline MELD score	8.9±2.7 (8)	9.8±2.5 (10)	0.05

TDF: Tenofovir disoproxil fumarate; ETV: Entecavir; LMV: Lamivudine; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; GGT: Gamma-glutamyl transpeptidase; INR: International normalised ratio; MELD: Model for end-stage liver disease.

Table 3. Virological response and ALT normalization during the antiviral treatment

Month	6		12		24		36		48	
	HBV DNA	ALT	HBV DNA	ALT	HBV DNA	ALT	HBV DNA	ALT	HBV DNA	ALT
Potent antiviral (TDF, ETV)	55/96 (57.3%)	34/55 (61.8%)	67/96 (69.7%)	36/55 (65.4%)	74/96 (77%)	40/55 (72.7%)	79/96 (82.2%)	41/55 (74.5%)	78/96 (81.2%)	42/55 (76.3%)
Weak antiviral (LMV)	13/24 (54.1%)	6/9 (66.6%)	12/24 (50%)	7/9 (77.7%)	10/24 (41.6%)	7/9 (77.7%)	9/24 (37.5%)	4/9 (44.4%)	9/24 (37.5%)	4/9 (44.4%)

HBV: Hepatitis B virus; ALT: Alanine aminotransferase; TDF: Tenofovir disoproxil fumarate; ETV: Entecavir; LMV: Lamivudine.

(range: 6–23), respectively. When admitted, three patients (2.5%) were diagnosed with HCC.

Virological Response (VR)

The median treatment duration was 60 months (19–156 months). Patients treated with weak antiviral agents were older than patients with potent antiviral agents (60.5±11.6 years vs 54.8±9.8 years, p=0.015) (Table 2). Baseline serum HBV DNA levels, ALT levels, and disease severity did not significantly differ between patients receiving weak and potent antiviral treatments (Table 2).

With ITT, the VR after 6 months, 1 year, 2 years, 3 years, and 4 years of potent antiviral treatments was 57.3% (55/96), 69.7% (67/96), 77.0% (74/96), 82.2% (79/96), and 81.2% (78/96), respectively, while the VR with weak antiviral treatments was 54.1% (13/24), 50.0% (12/24), 41.6% (10/24), 37.5% (9/24), and 37.5% (9/24) (p<0.001 for 2, 3, and 4 years of therapy). ALT normalization after 6 months, 1 year, 2 years, 3 years, and 4 years of potent antiviral treatment was 61.8% (34/55), 65.4% (36/55), 72.7% (40/55), 74.5% (41/55), and 76.3% (42/55), respectively. In comparison, ALT normalization with weak antiviral treatment was 66.6% (6/9), 77.7% (7/9), 77.7% (7/9), 44.4% (4/9), and 44.4% (4/9) (Table 3).

Serological Response

HBeAg loss was achieved in 30.4% of 23 HBeAg-positive patients while on antiviral treatment. The cumulative probability of HBeAg loss increased from 4.3% at 1 year to 18.7% at 4 years and 31.2% at 5 years of antiviral therapy (Fig. 1). HBeAg loss was slightly higher in patients treated with potent antiviral treatment than those treated with weak antiviral treatment (6.3% vs 4.2%, p=0.697). None of the patients had experienced HBsAg loss during the antiviral therapy.

Development of HCC

New HCC developed in 10 patients (8.5%, 10/117). The cumulative probability of the development of HCC was 2.6% at 1 year, 6.8% at 2 years, and 8.7% at 3 and 5 years of antiviral therapy (Fig. 2). Four of the ten patients received weak antiviral treatment, while six were on potent antiviral treatment. Three patients were diagnosed with HCC in the first year of the antiviral treatment, five in the second year, and two in the third year. At the time of the HCC diagnosis, seven patients had a detectable serum HBV DNA level, whereas the remaining three had VR (Table 4).

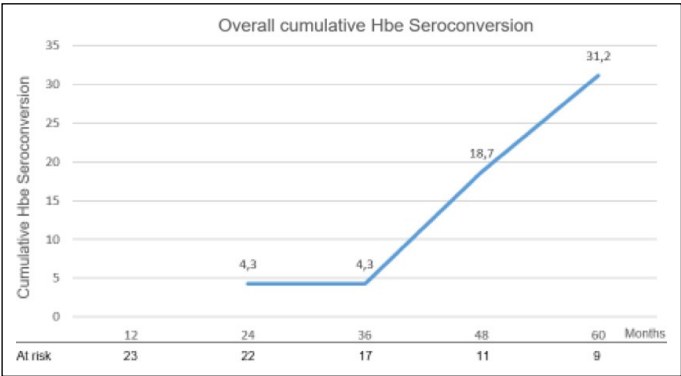


Figure 1. Cumulative probability of HBeAg seroconversion to antiHBe in patients with HBV-related cirrhosis while on antiviral treatment.

Table 4. Characteristics of patients who developed HCC during the follow-up period				
HCC development	Antiviral treatment	ALT level (U/L)	HBV-DNA level Log10 IU/ml	Liver disease
1. case	ETV	31	6.54	Decompensated
2. case	TDF	25	4.81	Compensated
3. case	TDF	34	4.11	Decompensated
4. case	TDF	25	–	Compensated
5. case	LMV	21	–	Decompensated
6. case	LMV	52	2.43	Decompensated
7. case	ETV	22	2.55	Decompensated
8. case	TDF	24	2.74	Decompensated
9. case	LMV	70	2.46	Decompensated
10. case	LMV	19	–	Decompensated

HCC: Hepatocellular carcinoma; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; TDF: Tenofovir disoproxil fumarate; ETV: Entecavir; LMV: Lamivudine.

MELD scores among patients treated with potent antiviral treatment significantly improved from baseline to week 60 (8.0±3.0 to 7.0±3.2, p=0.006, respectively).

Safety

Antiviral treatments were well tolerated. None of the patients discontinued antiviral therapy because of AEs. No significant difference in the mean baseline serum creatinine level between the two groups was observed (0.83±0.2 mg/dL vs 0.93±0.2 mg/dL, p=0.068). Serum creatinine levels among patients did not significantly change over time (0.83±0.20 mg/dL to 0.88±0.23 mg/dL, p=0.505 and 0.89±0.48 mg/dL to 0.85±0.22 mg/dL, p=0.575, respectively). Only four patients experienced a 0.5 mg/dL increase in serum creatinine levels at 5 years of the treatment.

The overall emergence rate of LMV resistance was observed in 15 of 24 patients treated with LMV. The cumulative probability of emergence of LMV resistance was 4.2% after 1 year, 8.3% at 2 years,

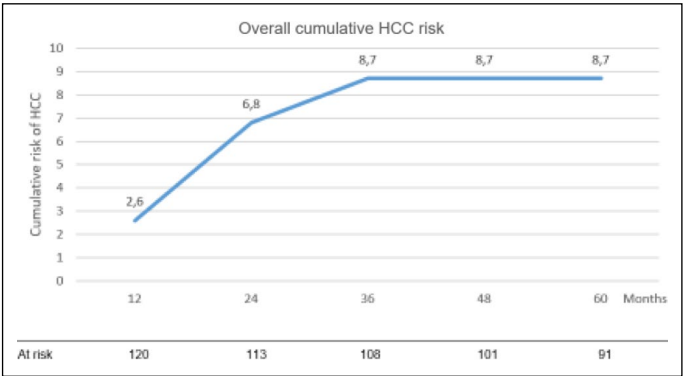


Figure 2. Cumulative probability of HCC development in patients with HBV-related cirrhosis over time.

25.6% at 3 years, 34.9% at 4 years, and 49.9% at 5 years of the treatment. TDF treatment was initiated in patients with an emergence rate of LMV resistance.

Decompensation was developed in 6 compensated patients treated with weak antiviral agents and 10 compensated patients treated with potent antiviral agents.

Overall, 29 patients died of causes considered unrelated to antiviral treatment. Among them, 19 patients were on potent antiviral treatment, whereas 10 were on weak antiviral treatment.

Discussion

This study demonstrates that long-term potent antiviral treatment, ETV or TDF, effectively suppressed HBV replication in patients with HBV-related cirrhosis. VR was significantly higher in patients treated with potent antiviral treatments than those treated with weak antiviral treatments. These findings are consistent with previous studies^[5,6,9,10] suggesting that ETV or TDF is effective in the long-term management of patients with HBV-related cirrhosis.

Previous studies have shown that the risk of progression to cirrhosis and the development of its complications strongly correlates with HBV viral load in CHB patients.^[11,12] Moreover, HBV viral suppression with antiviral therapy reduced the incidence of disease progression and improved the clinical outcome.^[7,8,13] Marcellin et al.^[14] demonstrated that long-term HBV viral suppression with TDF improved clinical outcomes and led to the regression of cirrhosis. Zou-tendijk et al.^[15] reported that a VR with ETV reduces the probability of developing clinical events in patients with HBV-related cirrhosis. This study confirms that long-term ETV or TDF, as potent antiviral agents, effectively suppressed viral replication in patients with cirrhosis and significantly improved clinical outcomes, as indicated by an improvement in the baseline MELD score.

The goals of effective antiviral therapy in HBeAg-positive CHB patients are HBeAg seroconversion to anti-HBe and, ultimately, HBsAg seroconversion to hepatitis B surface antibody (anti-HBs).^[17] HBsAg seroclearance predicts long-lasting viral suppression, diminishes disease progression, and improves clinical outcomes.^[7,16,17] HBsAg seroclearance is suboptimal under oral antiviral treatment.^[7,16–18] The present study achieved HBeAg loss in 30% of HBeAg-positive patients with cirrhosis. An increasing probability of HBeAg loss over time is observed. The results of this study are comparable to those of previous studies.^[16,17,19] Unfortunately, none of the cirrhotic patients had expe-

rienced HBsAg loss while on antiviral treatment. These results indicate that serological response was maintained and steadily increased through antiviral treatment periods.

Several studies have mentioned the association of high HBV viral load with the development of HCC.^[11,12,20–22] In the present study, the cumulative probability of the development of HCC increased from 2.6% at 1 year to 8.7% at 5 years of antiviral therapy. Ten patients were diagnosed with new HCC in the first 3 years of the antiviral treatment. HCC in these ten patients may have already developed before the antiviral therapy. HCC occurred more in nonresponding CHB patients or patients with viral breakthroughs than in those who experienced VR.^[22] At the time of the new HCC diagnosis, seven of the ten patients on antiviral treatment had a detectable serum HBV DNA level.

Oral antiviral agents were well tolerated in cirrhotic patients in the present study. None of the patients discontinued antiviral therapy because of AE. Serum creatinine levels remained stable during the treatment period.

Conclusion

In conclusion, potent antiviral treatment effectively maintains the virological response, reduces the incidence of disease progression, and improves the clinical outcome during the long-term follow-up of patients with HBV-related cirrhosis. Although HCC may still develop, it occurs at a lower rate. Long-term antiviral treatment can be safely continued in patients with HBV-related cirrhosis.

Ethics Committee Approval: The Ankara University School of Medicine Ethics Committee granted approval for this study (date: 13.01.2014, number: 01-04-14).

Author Contributions: Concept – GK, TG, EB, ZME, HG, RI; Design – GK, TG, EB, ZME, HG, RI; Supervision – GK, TG, EB, ZME, HG, RI; Materials – GK, TG, EB, ZME; Data Collection and/or Processing – GK, TG, EB, ZME; Analysis and/or Interpretation – GK, HG, RI; Literature Search – GK, TG, EB, ZME, HG, RI; Writing – GK, RI; Critical Reviews – GK, TG, EB, ZME, HG, RI.

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