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Efficacy and safety of entecavir and/or tenofovir in hepatitis B compensated and decompensated cirrhotic patients in clinical practice

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ABSTRACT

This study aimed to evaluate the efficacy and safety of entecavir and/or tenofovir in compensated (CC) or decompensated (DC) hepatitis B cirrhotic patients in real-life clinical practice. Of the 48 patients, included between April 2007 and March 2010, 12 were DC. The mean age was 55 ± 12.2 years, 85.4% were Caucasians and 8 patients were HBeAg positive. Mean viral load was 5.2 ± 1.9 $\log_{10}$ UI/mL. HBV-DNA undetectability at 3, 6, 12 and 24 months were 53.3%, 78.3%, 83.7% and 97.1%, respectively, similar in CC and DC. At 6 and 12 months, ≥ 80% of CC achieved ALT normalization, while only 42.9% and 71.4% in DC. After a median follow-up of 27.1 (0.7-45.3) months, 43 patients were Child Pugh Turcotte (CPT) class A (n = 39 at entry). In DC, progressive improvement in the MELD scores was observed: 12.73 (SD 4.5), 10.4 (SD 3.6) and 8.2 (SD 2.6), at baseline, 12 and 24 months, respectively. During follow-up, 7 patients died, 4 received liver transplantation and 5 developed hepatocellular carcinoma. In three out of four DC who died due to hepatic causes, these events occurred between the first 0.7 and 6.7 months, and all were CPT class C. Cumulative survival in CC *vs.* DC at 12 and 24 months were 94.4% *vs.* 66.7%, and 88.2% *vs.* 57.1%, respectively (log rank p = 0.03). No severe adverse events associated with entecavir or tenofovir were reported. In conclusion, in compensated and decompensated cirrhotic patients, entecavir and tenofovir were effective and well tolerated.

Key words. Tenofovir. Chronic hepatitis B. Cirrhosis.

INTRODUCTION

Approximately one third of the world's population has serological evidence of past or present infection with HBV, and 350 million people are chronically infected.[1] Cirrhosis, liver failure, and/or hepatocellular carcinoma (HCC) are expected to develop in 15-40% of patients with chronic hepatitis B (CHB).[2] Longitudinal studies of patients with CHB indicate that, after diagnosis, the 5-year cumulative incidence of developing cirrhosis ranges from 8 to 20%. The 5-year cumulative incidence of hepatic decompensation is approximately 20%, with the 5-year probability of survival being only approximately 14-35%. Patients with compensated cirrhosis have a better prognosis, with a probability of 80-86% survival rate at 5 years.[1,3,4]

The incidence and prevalence of CHB vary geographically; Spain is considered an area of intermediate endemicity (prevalence ranging from 2 to 7%).[5] Although the implementation of public health surveillance and immunization programmes in most European countries have reduced the burden of chronic HBV infection, the influx of foreign-born immigrants into the European Union from high endemic areas has contributed to a continued presence of chronic HVB infection.[6]

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It's been demonstrated that the suppression of HBV replication in a sustained manner is accompanied by reduction, and even improvement, in histological activity of chronic hepatitis.[7-9] Thus, it would be reasonable to expect that the use of potent antivirals would be associated with decreasing the risk of cirrhosis and HCC in non-cirrhotic patients and probably also, but to a lesser extent, in cirrhotic patients. In fact, current clinical practice guidelines advocate sustained HBV DNA suppression to reduce sequelae.[1,10,11] Nowadays, the drugs approved for CHB treatment are: immunomodulators (pegylated and standard interferon-α) or nucleos(t)ide analogs (NAs) (lamivudine [LAM], adefovir dipivoxil [ADV], telbivudine [LdT], entecavir [ETV], tenofovir disoproxil fumarate [TDF]). Of these, TDF and ETV are recommended oral first-line therapies for CHB.[1,10] In case of cirrhosis, the use of potent NAs with very low risk of resistance, i.e TDF or ETV, is particularly relevant in this group of patients, as long-term therapy is required with careful monitoring for resistance and flares. However, safety data of these agents in decompensated cirrhosis is limited.[1,12]

The aims of this study were to investigate the efficacy and clinical outcomes of ETV and/or TDF treatment in CHB patients with compensated or decompensated cirrhosis in real-life clinical setting. Safety and tolerability of the treatment were included as secondary objectives, such as the characteristics of this special population receiving ETV/TDF in Spain.

MATERIAL AND METHODS

Study population

Data were collected from 7 Spanish centers from a retrospective-prospective follow-up of HBV cirrhotic patients that were treated with ETV- or TDF-based antiviral therapy in routine clinical practice. The inclusion period lasted from April 2007, date of ETV launch in Spain, to March 2010, and final clinical data update was done until October 2011. Fifty one consecutive patients with CHB related cirrhosis were identified. Patients coinfected with other hepatitis viruses, or human immunodeficiency virus (HIV), were excluded from the study. Patients with previous solid organ transplantation were not eligible for study entry. Three patients were excluded from the final study population, two of them due to hepatitis D virus (HDV) and the other with hepatitis C virus (HCV) coinfection, so the final cohort were composed of 48 patients. The drug doses used were those approved for the treatment of chronic hepatitis B, TDF 300 mg/day, ETV 0.5 mg/day in naïve patients or 1 mg/day in NAs experienced-patients. Patients were either naïve to these two drugs (28 patients, 58.3%) or have been previously exposed to NAs (20 patients, 41.7%).

Demographic and liver disease data were collected, biochemical and clinical variables recorded, and the model for end-stage liver disease (MELD) score[13] and Child-Pugh-Turcotte- (CPT) score[14] were determined. The diagnosis of cirrhosis was established by liver biopsy or by a combination of clinical, biological and ultrasound findings. Two groups of patients were differentiated. Decompensated cirrhosis (DC) was defined as CPT score ≥ 7 points or the presence of a previous clinical episode of portal hypertension complication (variceal bleeding, hepatic encephalopathy or development of ascites). Compensated cirrhosis (CC) was defined as CPT score 5 or 6 points, class A, and no previous clinical episode of liver decompensation. From the 48 patients included, 36 were considered as CC and 12 patients as DC, 9 due to CPT score ≥ 7 points and 3 patients with stable disease but with previous portal hypertension complication (2 patients with previous episodes of ascites controlled by pharmacological therapy and 1 patient with previous variceal bleeding episode). None of the patients categorized as DC had additional cause of hepatic decompensation different from the evolution or portal hypertension complications associated with their liver disease. Diagnosis of HCC was established following the algorithm of the American Association for the Study of Liver Diseases (AASLD).[15]

Laboratory and radiological investigations, and follow-up studies

All patients were regularly monitored according to routine clinical follow-ups. Virological, biochemical, clinical and safety data were assessed during follow-up. Liver function tests, ALT and serological HBV markers were determined in all patients prior to the start of treatment, as well as serum HBV-DNA levels that were measured in each local laboratory using a quantitative real-time PCR assay with a maximum lower limit of detection of 20 UI/mL.

Imaging data such ultrasonography, spiral computed tomography or liver nuclear magnetic resonance were also collected. Both groups, DC and CC, were followed-up every 3-6 months, as defined in local clinical practice protocols for CHB patients at each participating hospital. During follow-up, virological,

biochemical and serological responses were assessed, and laboratory parameters were collected (HBV-DNA levels, ALT, HBsAg, HBeAg, Anti-HBe, CPT and MELD scores, serum creatinine, etc.). Abdominal ultrasonography was performed every six months as screening of HCC, and other radiological dynamic test were done at the discretion of the investigator. Clinical examination and counseling regarding treatment adherence were performed for all patients at each visit. Patients were followed until death, liver transplantation, loss to follow-up or the end of the study, with at least two years of follow-up since the initiation of treatment in each patient whenever possible.

Endpoints definitions

The main objective of the study was to investigate the efficacy and clinical outcomes of antiviral therapy with ETV and/or TDF in CHB patients with CC or DC in real-life clinical practice. Treatment efficacy was evaluated by measuring virological response, defined as HBV-DNA being undetectable (assessed by real-time PCR), and ALT normalization (≤ 1 ULN). Clinical outcomes evaluated were episodes of liver decompensation, diagnosis of HCC and death. Secondary objectives included safety and tolerability assessments and the characteristics of this special population receiving ETV and/or TDF in Spain.

Statistical analysis

Data were analyzed using descriptive statistics. Quantitative variables were expressed as the mean ± SE or median (range), and qualitative variables were expressed as frequencies. Categorical variables were compared using the Chi-squared test or Fisher's exact test; and continuous variables were compared using the t test or the Mann-Whitney U test when appropriate. Cumulative survival was evaluated by Kaplan Meier curves, with death or liver transplantation as event -patients were censored when loss from the study or at the end of follow-up-, and groups were compared by log rank test. Tests were two-tailed and p-values < 0.05 were considered significant. Analyses were performed using SPSS software (SPSS® 15.0; SPSS Inc., Chicago, Illinois, USA).

RESULTS

Patient demographics

The baseline characteristics are shown in table 1. Forty-eight patients were included, of which 12 were patients with DC. The mean age was 55 ± 12.2 years, 85.4% were Caucasians and 87.5% males (not statistically different between the CC and DC groups). As expected, the only characteristics statistically different between groups were those

Table 1. Baseline characteristics of the compensated and decompensated groups.

Characteristics	All patients (n = 48)	Compensated group (n = 36)	Decompensated group (n = 12)	P value
Age (years) (m ± SE)	55 ± 12.2	54.6 ± 12	56.2 ± 13.3	ns
Sex, n (%) Male	42 (87.5)	31 (86.1)	11 (91.7%)	ns
Race, n (%) Caucasian	41(85.4%)	30(83.3%)	11(91.7%)	ns
HBV DNA (log_{10} IU/mL) (m ± SE)	5.2 ± 1.9	5.25 ± 1.9	5 ± 2	ns
HBeAg-positive, n (%)	8 (16.7)	6 (16.7)	2 (16.6)	ns
Previous CHB NAs treatment, n (%)	20 (41.7)	16 (44.4)	4 (33.3)	ns
ALT (IU/L) med (r)	48.5 (14-517)	45.5 (14-243)	63 (24-517)	ns
Total bilirubin (mg/dL) (m ± SE)	1.24 ± 1.48	0.8 ± 0.4	2.7 ± 2.5	0.02
Albumin (g/dL) (m ± SE)	4 ± 0.6	4.2 ± 0.5	3.4 ± 0.6	0.001
INR (m ± SE)	1.1 ± 0.3	1 ± 0.1	1.4 ± 0.4	0.007
Platelet count (10^3/μL) (m ± SE)	128.1 ± 52	138.4 ± 50.2	94.2 ± 44.7	0.012
Creatinine (mg/dL) (m ± SE)	1 ± 0.3	1 ± 0.4	0.95 ± 0.1	ns
Child-Pugh-Turcotte score (points) (m ± SE)	5.85 ± 1.7	5.14 ± 0.3	8 ± 2.2	0.001
MELD score (m ± SE)	8.5 ± 3.6	7.23 ± 2	12.73 ± 4.5	0.002
Ascites, n (%)	9 (18.8)	NA	9 (75)	NA
Episodes of hepatic encephalopathy, n (%)	2 (4.2)	NA	2 (16.7)	NA
Episodes of variceal bleeding, n (%)	2 (4.2)	NA	2 (16.7)	NA

NAs: nucleot(s)id analogs. CHB: chronic hepatitis B. HBV: hepatitis B virus. m ± SD: mean ± standard error. med (r): median (range). NA: not applicable. ns: not significant.

Table 2. Virological and biochemical responses during ETV and/or TDF therapy.

Characteristics	All patients	Compensated group	Decompensated group
• HBV DNA undetectable n (%)			
3 months	24/45 (53.3)	18/35 (51.4)	6/10 (60)
6 months	36/46 (78.3)	29/36 (80.6)	7/10 (70)
12 months	36/43 (83.7)	29/35 (82.9)	7/8 (87.5)
24 months	33/34 (97.1)	26/27 (96.3)	7/7 (100)
• Normalization of ALT n (%)			
6 months	29/36 (80.6)	26/29 (89.7)	3/7 (42.9)
12 months	30/38 (78.9)	25/31 (80.6)	5/7 (71.4)
24 months	26/33 (78.8)	21/26 (80.8)	5/7 (71.4)
• HBeAg n (%)			
Loss	2/8 (25)	1/6 (16.7)	1/2 (50)

HBV: hepatitis B virus.

associated with hepatic function or portal hypertension.

As in clinical practice, co-morbid features were frequent. Seventeen patients had previous history of significant alcohol consumption, 9 patients were diabetics –both characteristics similarly distributed between groups–, and 7 patients, all of them with compensated cirrhosis, had arterial hypertension.

Twenty patients have been treated previously with NAs that were equally distributed in both groups (44.4% and 33.3%, in CC and DC, respectively). The previous treatment was LAM in 6 patients, ADV in 6 and the combination of both in the other 8 patients. The main causes of treatment change were virological breakthrough (11 patients, 8 in CC group and 3 in DC group), partial response (3 in the CC and 2 in the DC group), renal function deterioration (2 patients, both with ADV treatment changed to ETV), economic reasons (2 patients who were on ADV or ADV plus LAM were changed from ADV to TDF). The last 4 patients belonged to the CC group.

Fourty-two patients were on monotherapy (33 with ETV and 9 with TDF), and 6 patients received combination therapy (3 with TDF plus LAM, and 3 with ETV plus TDF).

Virological, biochemical and serological responses

ETV or TDF-based antiviral treatment was effective in cirrhotic patients, both in the CC and DC groups, with 78.3% of patients achieving undetectable HBV-DNA at 6 months, and 83.7% after 12 months of treatment, as shown in table 2. Nearly all patients with HBV-DNA determination had achieved a virological response at 24 months. The four patients in which ADV treatment was changed –in two cases to ETV because of renal failure, and in the other two patients to TDF due to economic reasons, maintained HBV-DNA undetectability from baseline through the entire period of the follow-up.

Almost 80% of the patients with an elevated ALT at baseline (n = 30, 62.5%) achieved a biochemical response during any time-point of the follow-up, as shown in table 2. ALT normalization seemed to be more rapid in the CC *vs.* DC group (90% *vs.* 42% at 6 month; and 80% *vs.* 71.4% at 12 and 24 months, respectively).

Only 8 patients (6 in CC group) were HBeAg positive. One patient lost HBeAg in each group (25% of the HBeAg positive patients). However, no HBeAg seroconversion was achieved in any patient. HBeAg positive patients had a similar virological response rate as HBeAg negative at the last follow-up, although more patients achieved a rapid HBV-DNA undetectability in the latter group (at 6 months 50% *vs.* 84.2%, p = 0.033; at 12 months 75% *vs.* 85.7%, p = 0.46; and at 24 months 100% *vs.* 96.7%, p = 0.7).

Virological response was not different between naïve patients and NAs-experienced, at 6 months (84.2% *vs.* 74.1%, p = 0.4), 12 months (82.4% *vs.* 84.7%, p = 0.8) and 24 months (93% *vs.* 100%, p = 0.22), respectively. The early change in NAs treatment in the context of virological breakthrough may partially explain the potent virological response and lack of difference from that of the naïve patients (HBV DNA [mean ± SD]: 5.35 ± 2 $\log_{10}$ in naïve *vs.* 4.9 ± 1.8 $\log_{10}$, in NAs-experienced patients, p = 0.44).

When virological responses were analyzed in the cohort of patients receiving monotherapy, no statistical differences between ETV and TDF treatments were observed (HBV-DNA at 3, 6, 12 and 24 months:

48.4% *vs.* 62.5%, p = 0.69; 74.2% *vs.* 77.8%, p = 1.00; 80.6% *vs.* 100%, p = 0.57; 96% *vs.* 100%, p = 1.00; respectively).

Changes in hepatic function during antiviral therapy

The DC group was comprised of 12 patients and characterized by more advanced cirrhosis in comparison to the CC group, as shown in table 1. Gastroesophageal varices were also more frequently present in the DC *vs.* CC group (75% *vs.* 36.1%, [p = 0.01]). Liver function improved in 4 out of 9 patients with baseline CPT score ≥ 7 points (class B, 7 points in 3 and 9 points in 1 patient) to CPT class A at the end of the follow-up (5 points of improvement was noted in 3 patients). CPT class was not improved to class A in 5 out of the 9 patients with a baseline CTP score ≥ 7 points. Four out of these 5 patients presented further episodes of liver decompensation. Three of these patients had a baseline CPT class C (13, 14 and 11 points, respectively) and died prematurely in 0.7, 1.5 and 6.7 months after the initiation of antiviral therapy. The third patient with > 6 months follow-up had undetectable HBV-DNA at 6 months. The fourth patient with CPT class C (10 points) received liver transplantation at month 5.3 without any change in the CPT score. Finally, one patient with baseline CPT class B (7 points) that was still alive at 21.5 months of follow-up had not shown improvement in CPT score (this patient reported significant alcohol consumption).

The three patients in the DC group, categorized as such due to previous portal hypertension complication, maintained adequate liver function and did not develop new episodes of liver decompensation.

No patient in the CC group developed liver decompensation during follow-up. When evaluating CPT score improvement in the entire cohort, there was 39 patients with baseline class A (32 with 5 points and 7 patients with 6 points) and after a median follow-up of 27.1 (0.7-45.3) months, 43 patients were CPT class A (5 and 6 points in 37 and 6 patients, respectively).

Stable MELD scores were observed in the CC group during follow-up, while MELD scores progressively improved in the DC group throughout the follow-up (12.73 [SD 4.5] at baseline, 10.4 [SD 3.6] at month 12 and 8.2 [SD 2.6], at month 24 months).

On-treatment outcomes

All patients were followed since the initiation of antiviral treatment until death, liver transplantation (LT) or the end of follow-up period, at least for 24 months whenever possible. The median time of follow-up was 27.1 (0.7-45.3) months. There was no statistical difference in the time in follow-up between the two groups (CC group 28.4 [8.6-45.3] months *vs.* DC group 23.3 [0.7-42] months; p = 0.1).

During the follow-up, 7 patients died (14.6%) and 4 patients received a LT (8.3%). Death in the three patients of the CC group was due to HCC, bladder neoplasia and other non-hepatic cause. Four patients died in the DC group, 2 patients of hepatic liver failure, another one of HCC and the last patient with Down syndrome secondary to surgical complications of an intestinal obstruction.

Three out of 4 patients who received LT were from the CC group and indication was in relation to development of HCC, two cases diagnosed after and one before the start of antiviral therapy. The fourth patient who received a LT was from the DC group, due to liver failure and portal hypertension complications.

As expected, the cumulative LT-free survival was better in the CC group than in the DC group (94.4% *vs.* 66.7% at month 12, and 88.2% *vs.* 57.1% at month 24, log rank p = 0.03) (Figure 1). When liver-related mortality was evaluated, censoring non liver-related deaths, the statistical difference between groups was maintained (94.4% *vs.* 66.7% at month 12, and 91% *vs.* 66.7% at month 24, log rank p = 0.043).

Six patients were diagnosed with HCC before the initiation of the antiviral therapy and all received curative treatment (surgical resection, radiofrequency ablation or LT). Five new cases were diagnosed during follow-up. Three cases were diagnosed in the CC group at month 4, 15 and 17. One patient received LT, another died of HCC progression and one was treated and alive at the end of follow-up. In the DC group two cases were diagnosed at month 5.2 and 22, the first one died after 1.5 months since the diagnosis and the other one was alive at the end of the follow-up.

Safety

There were no serious adverse events associated with antiviral treatment. Only two patients developed mild headache and dyspepsia during the first weeks of treatment, which resolved without sequelae. None of the patients developed clinically evident lactic acidosis, but lactate was not routinely measured. No ALT flares were observed.

No significant deterioration of renal function was observed during antiviral treatment and no patient

experienced an elevation in serum creatinine levels of ≥ 0.5 mg/dL. In the two patients with antiviral treatment changed from ADV to ETV because of renal failure, renal function remained stable with no further deterioration. No significant difference in serum creatinine levels was noted between baseline and follow-up or between ETV or TDF treatment.

DISCUSSION

The availability of potent orally administered antiviral agents against HBV, with favorable safety profile and high barrier to resistance, has changed the management of CHB. However, unmet medical needs are still substantial in the management of compensated and decompensated cirrhotic patients.[1] Results of this study confirm that ETV and TDF are effective and well tolerated in HBV-related cirrhotic compensated or decompensated patients. Efficacy and safety data has previously been published in this patient population using other NAs, such as LAM, ADV or LdT.[16-18] Studies with LAM, the first NA introduced in the treatment of CHB, in cirrhotic patients have proven the principle that viral suppression, improved hepatic function, and reduced morbidity could be achieved in this patient population without serious adverse effects.[19-22] However, the high viral resistance rate to LAM resulted in a progressive loss of this beneficial outcome.[23] On the other hand, the antiviral effects of ETV and TDF in cirrhotic patients with hepatic decompensation in the clinical practice setting have not been definitely established.[1] Four recent studies have reported the use of these new generation antiviral therapies in CHB patients with decompensated liver disease, with varying patient characteristics and study designs.[24-27]

The present study, using real-time PCR assay, showed potent inhibition of HBV replication, with undetectable HBV-DNA achieved in 70%, 87.5% and 100% of the decompensated patients after ETV and/or TDF treatment at 6, 12 and 24 months, respectively. Normalization of ALT levels was also observed in 71.4% of the patients at month 12 and 24. Virological response was not different between AN-experienced and naïve patients. Previously reported studies conducted with ETV (0.5 mg) have demonstrated high antiviral efficacy: undetectable HBV DNA in 87.1% of the patients at 48 weeks of therapy, as published by Shim, *et al.,* while other studies have reported more modest response rates.[25,26]

Recently, Liaw, *et al.* published the first report on the safety and efficacy of TDF in decompensated HBV patients.[27] While the primary endpoint of the study was evaluating safety, the authors demonstrated in a 48 week interim analysis that TDF, TDF/FTC and ETV achieved undetectable HBV-DNA in 70.5%, 87.8% and 72.7% of the patients, respectively. In our study, only few patients treated with TDF were included. Although no differences in virological

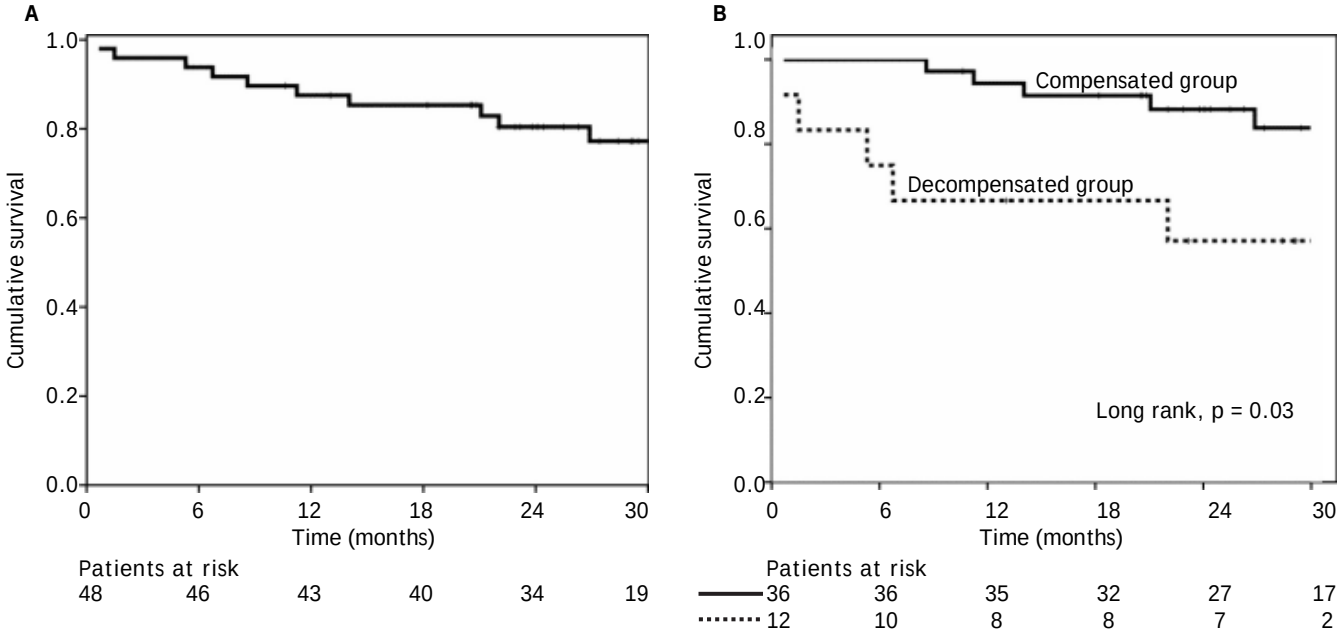

Figure 1. *Cumulative survival without liver transplantation of all patients (**A**) and compensated and decompensated groups (**B**).*

responses between ETV and TDF therapies were observed in this cirrhotic cohort, this comparison must be interpreted with caution due to the small patient numbers.

Clinical outcome in HBV-related cirrhotic patients is an important aspect of antiviral therapy. As we previously commented there were different populations included in the studies with decompensated cirrhosis and in our study. In any case, our decompensated patients are different from our compensated cohort as is observed not only in CPT and MELD scores, also in previous episodes of liver decompensation and presence of gastro-esophagic varices, events recognized in a dynamic view of cirrhosis as more advances stages with pour outcome.[28,29] In the previously mentioned study of Liaw, *et al.*,[27] CPT and MELD scores improved after TDF, TDF/FTC and ETV treatment in each group. A decrease of > 2 points in CPT score was achieved in 25.9%, 48% and 41.7% of the patients, respectively, at week 48. In our study, none of the patients in the compensated group suffered an episode of liver decompensation. In the decompensated group, 7 out of 12 patients maintained or achieved CPT class A. In the other five patients that not reached a compensated liver disease, four of them were CPT class C. It is possible that improvement in clinical outcomes is not evidenced when liver function is too impaired, even if inhibition of HBV replication is achieved. These results are comparable to the study of Shim, *et al.*,[24] in which nearly 50% of patients had a clinically significant decrease in CPT score of > 2 points after 12 months of ETV therapy; nevertheless, not all decompensated patients had improvement in their liver function. This assumption is supported by previously reported data in studies with LAM.[30] Liaw, *et al.*, has also demonstrated that CPT score was improved or stabilized in approximately two-thirds of subjects treated with ETV or ADV.[25] When liver function was evaluated by using the MELD score, a progressive improvement in liver function was noted in decompensated patients at 12 and 24 months of follow-up in our study.

HCC development is an important step in the natural history of cirrhosis, being the principal cause of mortality in these patients. In our study, after antiviral treatment initiation, HCC was detected in 5 patients (10.4%), with a similar incidence rate than reported in other studies.[24,25] As expected, the cumulative survival rate without liver transplantation was superior in the compensated group. However, patients in the decompensated group presented with a greater than 50% survival at 24 months. The mortality rate in the decompensated group was 33% (4/12) in which 3 out of 4 patients with impaired baseline liver function died prematurely during follow-up due to liver complications.

Both ETV and TDF were well tolerated, similarly as demonstrated in other studies, without any renal function deterioration.[24,25,27] Lactic acidosis has been reported in decompensated cirrhotic patients.[31] Nevertheless, in line with the study of Shim, *et al.*, no lactic acidosis was observed in our study.[24] Liaw, *et al.* reported one case of lactic acidosis in an ETV-treated patient that resolved without withdrawal of ETV therapy.[25]

Our study has some limitations. The sample size of the cohort was small. A balanced representation of the different treatment regimens and stratification according to relevant clinical variables was not possible in this real-life observational study. As ETV was available for clinical use earlier than TDF, the number of patients included with TDF therapy is considerably lower. Although inclusion of patients treated in clinical practice results in greater heterogeneity of the baseline characteristics, these results are more representative to the daily work of a physician. In general, the participating hospitals followed the clinical guidelines and recommendations. On the other hand, clinical heterogeneity in patient care cannot be ruled out. The duration of the observation period in this report is relatively short. However, the study is ongoing and aims to collect further information in this patient population, in which long-term follow-up data is scarce.

In summary, the present study provides evidence that treatment with ETV or TDF treatment is effective and well tolerated in cirrhotic HBV patients, with or without decompensated liver disease. In addition, ETV and TDF could improve liver function, especially in decompensated cirrhotic patients. Additional data with higher patient number and longer follow-up period is necessary to confirm these results.

ABBREVIATIONS

- **ADV:** adefovir dipivoxil.
- **CC:** compensated cirrhosis.
- **CHB:** chronic hepatitis B.
- **CPT:** Child Pugh Turcotte.
- **DC:** decompensated cirrhosis.
- **ETV:** entecavir.
- **HBV:** hepatitis B virus.
- **HCC:** hepatocellular carcinoma.
- **LAM:** lamivudine.

- **NAs:** nucleos(t)ide analogs.
- **TDF:** tenofovir disoproxil fumarate.

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