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The impact of newer nucleos(t)ide analogues on patients with hepatitis B decompensated cirrhosis

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Abstract

Background/aim Patients with HBV-related decompensated cirrhosis (HBV-DeCi) should be treated with potent nucleos(t)ide analogues (NA)[entecavir (ETV) or tenofovir (TDF)]. The aim was the evaluation of safety and efficacy in terms of changes in liver disease course in HBV-DeCi patients treated with ETV or TDF.

Methods In 52 HBV-DeCi patients clinical and laboratory data, including glomerular filtration rates (GFR), were recorded. The changes in MELD (DMELD) and Child-Pugh (DCTP) scores between baseline and after 6 months of treatment were evaluated. The independent factors associated with survival were evaluated.

Results 31 patients under TDF and 21 under ETV were evaluated. During a median follow-up of 22.5 months (range: 6-68), there were no differences between the two groups in GFR and serum phosphate levels. At the end of follow up, in the TDF group, 2 patients died and 3 received liver transplantations (LT), while in the ETV group, 1 patient died and 3 received LT. In multivariable Cox regression analysis, DMELD was independently associated with the outcome in the total cohort (HR: 1.78, 95%C.I.:1.12-2.79, P=0.013) as well as in the subgroup of naïve (n=37) patients (HR: 1.8, 95%C.I.:1.19-4.5, P=0.03). Finally, in the non-hepatocellular carcinoma patients, the DCTP score was independently associated with the outcome in the total cohort (HR: 2.64, 95%C.I.: 1.21-7.29, P=0.015).

Conclusions TDF and ETV appear to have similar renal safety profile in HBV-DeCi patients. DMELD score in the total cohort and DCTP score in non-HCC patients were independently associated with the outcome; these findings need confirmation in larger studies.

Keywords Decompensated cirrhosis, nucleos(t)ide analogues, entecavir, tenofovir

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Introduction

It is estimated that more than half a million people with hepatitis B virus (HBV) infection die annually due to complications of liver decompensation and/or hepatocellular carcinoma (HCC) [1]. Untreated patients with HBV decompensated cirrhosis (HBV-DeCi) have a 5-year survival rate of only 14%-35% [2]. Oral nucleos(t) ide analogues are the only anti-viral agents used in patients with HBV-DeCi and should be instituted regardless of serum HBV DNA levels in order to improve liver dysfunction and survival [2,3]. Studies with lamivudine and adefovir have shown improvements in the clinical outcomes of patients with HBV-DeCi [2,4], but both agents have several drawbacks including low antiviral potency and viral resistance followed by virological and biochemical breakthroughs [2,5,6]. The newer nucleos(t) ide analogues (NAs) [i.e. entecavir (ETV) and tenofovir (TDF)] are potent antiviral agents with a minimal or even

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Conflict of Interest: None

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nonexistent risk of resistance and therefore they represent the currently recommended first-line for the therapy of HBV-DeCi patients [3].

Safety profile of NAs is an important issue with their effect on renal function being of particular concern in the difficult-to-manage patients with HBV-DeCi. Although the nephrotoxic potential is considered to be higher for nucleotide analogues [7,8], similar rates of renal adverse events were observed after one year of therapy with TDF, TDF plus emtricitabine or ETV in a recent randomized trial including patients with HBV-DeCi [9]. However, there are still concerns about the potential nephrotoxicity of TDF mostly based on reports from patients with human immunodeficiency virus (HIV) infection, for whom TDF has been licensed for longer and decline of creatinine clearance and proximal tubular dysfunction with occasional Fanconi syndrome with hypophosphatemia have been reported [10,11].

Although the majority of patients with HBV-DeCi should be referred for liver transplantation (LT), the wide use of antiviral therapy may reverse hepatic dysfunction or failure [12-15], leading in some cases to withdrawal from the LT listing [16,17]. However, a significant proportion of HBV-DeCi patients die or require LT despite the use of antiviral treatment [6]. Physicians usually rely on reasonable clinical judgment and decide on an individual basis, but more objective criteria could be more helpful to determine the outcome of patients with HBV-DeCi who receive ETV and TDF, currently the optimal anti-HBV agents [3].

The aim of this retrospective study was to assess in ETV and TDF treated patients with HBV-DeCi: a) the safety of long term treatment with the 2 antiviral agents regarding renal function, b) the efficacy in terms of virologic response and changes in severity of liver disease, and c) to evaluate the prognostic factors of their outcome.

Patients and methods

All adult HBV-DeCi patients from 5 Greek centres who were treated with NAs (i.e. ETV or TDF) starting from 2007 were evaluated retrospectively. To be eligible, HBV-DeCi patients had to use NAs for 6 or more months from baseline unless a liver-related event (e.g. death or LT) or a NAs-related adverse event had caused NAs discontinuation. The baseline was defined as the date of starting NAs in naïve patients or conversion to the two NAs (ETV or TDF) in patients who were already under other oral antiviral therapy. Patients with hepatocellular carcinoma (HCC) were not excluded in safety analysis, while two separate analyses for the outcomes in patients with or without HCC were performed providing that the HCC patients were alive, died from non-HCC causes or underwent LT during the follow up period.

Decompensated cirrhosis was defined by the development of any complication of portal hypertension (ascites, variceal bleeding, or hepatic encephalopathy) and/or the Child-Pugh (CTP) score more than 7. The presence of ascites was detected by clinical examination and imaging techniques (ultrasound or computer tomography). None of the patients had previous liver or other organ transplantation. Patients were excluded for HIV- and hepatitis C virus-positive serologies, hepatitis D co-infection, alcohol abuse or use of hepatotoxic or nephrotoxic drugs including those affecting renal tubular secretion before NAs initiation or during the follow-up period.

At baseline, for each patient, demographic and clinical data were recorded including age, sex, previous antiviral therapy, presence of HCC and concomitant diseases (e.g. diabetes mellitus, coronary artery disease). Regarding laboratory data, creatinine, blood urea, phosphate, protein, albumin, bilirubin and clotting profile based on INR. Child-Pugh (CTP) and model for end stage of liver disease (MELD) scores were recorded at baseline, at the 6- and 12-month visits, and the final visit of the follow-up period. In addition, HBV DNA and serological indexes (HBsAg and anti-HBs/anti-HBe status) was recorded at baseline, at 12 months and at the end of follow up. HBV DNA was evaluated for all patients by sensitive real time PCR with lower level of detection <45 IU/mL (COBAS TaqMan, Roche Molecular Systems). Data recorded during follow-up included: a) cirrhosis-related complications [variceal bleeding, ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, hepatic encephalopathy, HCC] and the time from baseline which were occurred, and b) the response to NAs and NAs-associated adverse events. In addition, assessment of renal function was performed based on serum creatinine and estimated glomerular filtration rate (eGFR) using the creatinine-based 4 variable MDRD formula. The mathematical equation for eGFR was used as followed: modification of diet in renal disease (MDRD) formula ($mL/min/1.73m^2$)=$186 \times (Creatinine)^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female) $\times$ (1.210 if black) [18]. At the last visit, the clinical status was evaluated (alive, death or liver transplantation) and the cause of death was recorded.

The primary study objective was to evaluate the safety/tolerability of NAs (i.e. TDF and ETV) in the treatment of HBV-DeCi patients regarding renal function and their efficacy and impact on the course of liver disease, as well as to assess the prognostic factors related to the outcome (i.e. death or LT). The severity of liver disease was evaluated with the CTP score and MELD score, which were used as published [19,20]. The changes in MELD (DMELD) and CTP score (DCTP) between baseline and after 6 months were also evaluated.

Statistical analysis

All data were analysed using the statistical package SPSS (version 19.0 SPSS Inc, Chicago, IL). Univariate comparisons of demographic and baseline clinical factors were performed using Mann-Whitney U tests for continuous variables and Chi-square tests for categorical variables. Paired T test or Wilcoxon matched-paired test were used for the comparisons between the variables at different time points. The patient survival according to different antiviral agents was calculated using Kaplan-Meier analysis and compared with the log rank sum test. Univariate and multivariable Cox regression analyses were performed to identify predictive factors for

outcome (i.e. death or LT) in patients with HBV-DeCi. The multivariable analysis was performed using variables with P<0.1 in the univariate analysis. The discrimination ability of the independent factors to predict the outcome was evaluated by using the area under a receiver operating characteristic curve (AUC) [21]. A two-tailed P value less than 0.05 was considered to be statistically significant.

Results

Baseline characteristics

A total of 52 patients (33 males, age: 59±10 years) with HBV-DeCi were enrolled in the present study. The baseline characteristics of these patients are summarized in Table 1. All patients were HBeAg negative, and the median HBV DNA level was 15,200 (range: 0-128x10^6) IU/mL. The mean CTP and MELD scores were 8.1±1.7 and 12.1±3.8 respectively, while 7 (14%), 39 (75%) and 6 (11%) patients were classified as CTP class A, B and class C respectively. Among the 7 patients of CTP class A, 4 had a history of ascites and 3 of variceal bleeding. TIPS placement was performed in none of the patients.

Fifteen patients were already started on antiviral therapy (lamivudine ± adefovir) before enrollment in the present study and they were switched to ETV or TDF (2 patients with viral breakthrough to lamivudine and 13 patients after decision of attending physician), while 37 patients were NAs naïve, i.e. antiviral therapy was initiated at baseline (Table 1). Twenty-one patients (41%) were treated with ETV and 31 (59%) patients with TDF. The baseline clinical and biochemical characteristics were not significantly different between ETV and TDF treated patients (Table 1, all P values >0.10), except for a trend for a smaller proportion of NAs naïve patients in the TDF than in the ETV group (19/31 or 61% vs 18/21 or 86%, P=0.087).

Table 1 Baseline clinical and laboratory characteristics of 52 patients with HBV decompensated cirrhosis in our cohort

Variable (unit)	All patients, (n=52)	ETV group (n=21)	TDF group (n=31)
Age, (mean±SD), years	59±10	58±9	60±10
Sex, men n, (%)	33 (63)	14 (66)	19 (61)
Hepatocellular carcinoma n, (%)	6 (12)	4 (19)	2 (7)
Diabetes mellitus, n, (%)	5 (10)	3 (14)	2 (6)
Duration of previous antiviral treatment before baseline, (median, range) months	53 (5-144)	36 (14-48)	60 (5-144)
Follow up period, (median, range), months	22.5 (6-68)	18 (7-68)	25 (6-66)
Chid-Pugh (CTP) score (mean±SD)	8.1±1.7	7.9±0.9	8.3±1.9
MELD score, (mean±SD)	12.1±3.8	11.9±3.6	12.2±3.9
ALT levels (mean±SD), IU/L	67±38	75±34	57±40
AST levels (mean±SD), IU/L	76±37	82±35	63±44
Albumin (mean±SD), g/dL	3.3±0.6	3.2±0.6	3.3±0.6
HBV DNA (median, range), IU/mL	15,200 (0-128×10^6)	36,650 (0-128×10^6)	5,920 (0-2.3×10^6)
Antiviral therapy before baseline, n, (%)*			
Lamivudine (±adefovir)	15 (29)	3 (14)	12 (39)
Naïve	37 (71)	18 (86)	19 (61)

*All P values were >0.10 except for a trend for a smaller proportion of NAs naïve patients in the TDF than ETV group (P=0.087) *ETV, entecavir; TDF, tenofovir; CTP, child-pugh score; MELD, model for end stage of liver disease*

Changes in renal function

In all patients, eGFR was 88±28, 87±25, 83±20 and 81±23 mL/min at baseline, 6, 12 months and last follow up, respectively (P value >0.05 for all comparisons). The proportion of patients with eGFR <50 mL/min at baseline, 6, 12 months and last follow up were 5.7%, 7.7%, 7.7% and 9.6%, respectively. Finally, eGFR was not different between TDF and ETV groups of patients at baseline, at 6 months, at 12 months and last follow up, and this was also true in the 37 patients who were started on antiviral agents at baseline (Fig. 1). The proportion of patients with eGFR <50 mL/min in TDF and ETV groups at baseline, 6, 12 months and last follow up were 6.5% vs 4.7%, 6.5% vs 9.5%, 6.5% vs 9.5% and 9.7% vs 9.5%, respectively (P value >0.05 for all comparisons). In these patients with eGFR<50 mL/min, adjustment of NA dosage was performed with administration every 48 or 72 hours according to the severity of renal function.

In the total group of patients, serum phosphate levels at baseline, 6 and 12 months (not available at last follow up due to the small number of available data) were 3.1±0.5, 3.1±0.5 and 3.1±0.3, respectively (P value >0.05 for all comparisons). None of the patients developed serum phosphate <2.0 mg/dL during the follow up period. Finally, phosphate levels were not different between TDF group and ETV group at baseline, at 6 and 12 months (P>0.05). Both antivirals were well tolerated and none of the patients discontinued therapy.

Virologic and serologic responses

All patients of both groups had undetectable serum HBV DNA at 12 months and at the end of follow-up. There was no viral breakthrough in any patient. Regarding HBV serology, no

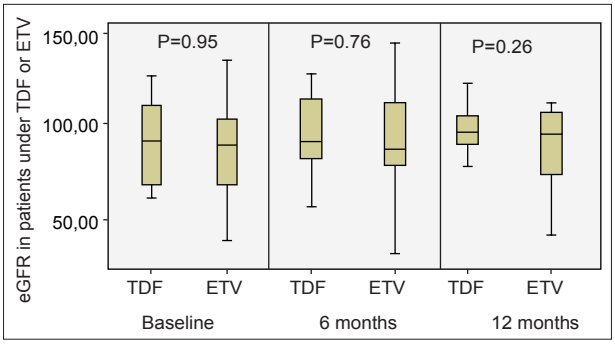

Figure 1 Evolution of estimated glomerular filtration rate (eGFR) in naïve patients (n=37) with HBV decompensated cirrhosis under nucleos(t)ide analogue [entecavir (ETV) or tenofovir (TDF)]

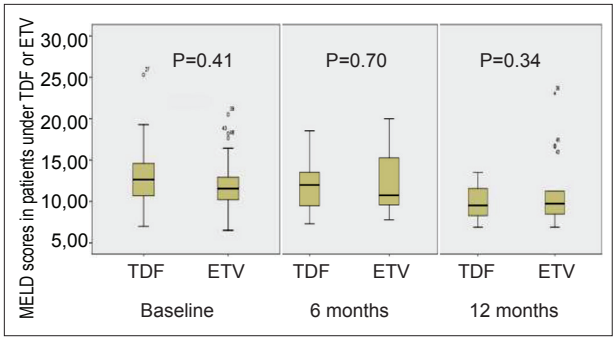

Figure 2 Evolution of model for end stage liver disease (MELD) score in naïve patients (n=37) with HBV decompensated cirrhosis under entecavir (ETV) or tenofovir (TDF)

patient had HBsAg clearance, while they all remained HBeAg negative during follow-up period.

Changes in severity of liver disease (MELD score and CTP score)

In the total group of patients, MELD scores at baseline, 6, 12 months and last follow up were 12.1±3.8, 11.6±3.3, 10.6±3.2 and 11.3±3.9, respectively, with no difference at any time point (P>0.05); in the TDF group of patients: 12.2±3.9, 11.3±2.9, 10±2 and 11±3.6, respectively [P>0.05 for all comparisons except for the MELD score at 12 months, which was significantly lower, compared to the MELD score at baseline (P=0.035)]; in the ETV group of patients: 11.9±3.6, 11.8±3.7, 11.5±4.2 and 11.6±4.3, respectively (always P>0.05);. In the total cohort, the MELD scores at different time points were not different between TDF group and ETV group of patients (always P>0.05), and this was also true when only the 37 naïve patients at baseline were evaluated (Fig. 2).

In the total group of patients, CTP scores at baseline, 6, 12 months and last follow up were 8.1±1.7, 7.3±1.2, 7.2±1.2 and 7.8±1.6, respectively, with no difference at any time point (P>0.05 with a trend for lower CTP score at 12 months compared to the baseline (P=0.064)]; in the TDF group of patients: 8.3±1.9, 7.1±1.1, 7.1±0.9 and 7.9±1.5, respectively (always p>0.05); in the ETV group of patients: 7.9±1.1, 7.4±1.3, 7.3±1.3 and 7.7±1.4, respectively (always P>0.05). In the total cohort, the CTP scores at different time points were not different between TDF group and ETV group of patients (always P>0.05), and this was also true when only naïve patients or non-HCC patients were evaluated. Finally, 11 (21%) of the 52 patients had reduction in CTP score ≥2 at 12 months, compared to the baseline, with no difference between TDF and ETV group of patients [6/31 (19.3%) vs 5/21 (23.8%), P=0.29]

Clinical course

Clinical failure of antiviral treatment was observed in 9 (17%) patients because of death (n=3) or LT (n=6). None of the patients died or underwent LT during the first 6 months. There were 48 and 46 patients alive without LT at 18 and 24 months, respectively. In the TDF group, 2 patients died and 3 received LT, while in the ETV group, 1 patient died and 3 received LT. The causes of death were sepsis in two patients (11 and 25 months from baseline in ETV and TDF group, respectively) and HCC/liver failure in one patient (18 months from baseline in TDF group). Two patients received LT between 7 and 12 months, 2 patients between 13 and 24 months and 2 patients between 25 and 56 months. The cumulative survival rates did not differ between TDF and ETV groups (survival at 5 years: 63% vs 73%, P=0.65).

Regarding new complications during follow-up, 4 patients developed HCC (all under TDF at 4, 6, 34 and 52 months, respectively from baseline) and 2 patients developed new onset ascites (1 under TDF at 24 months from baseline and 1 under ETV at 46 months from baseline, possibly related with progression of the underlying liver disease). There were no differences in complication rates between TDF and ETV group of patients (P=0.29).

Predictive factors for the outcome

When both baseline and 6-month characteristics were analyzed, in the univariate Cox regression analysis, age (P=0.035), ALT at baseline (P=0.042), MELD score at 6 months (P=0.034), and changes of MELD and CTP scores from baseline to 6 months (P=0.031 and P=0.035, respectively) were significantly associated with the outcome (i.e. death or LT) (Table 2). These variables were included in the multivariable Cox regression analysis, in which only changes of MELD score (DMELD) was independently associated with the outcome (HR; 1.78, 95% C.I.: 1.12-2.79, P=0.013) (Table 2). The AUCs for DMELD score from baseline to 6 months was very good (AUC: 0.82, 95% C.I.: 0.67-0.92) (Fig. 3). The best cut off point for DMELD score was 0.12 giving a sensitivity 86%, specificity 78%, PPV 0.43 and NPV 0.97 (Table 3). However, when only the non-HCC patients (n=46) were evaluated, changes of CTP score (DCTP) from baseline to 6 months (HR: 2.64, 95% C.I. 1.21-7.29, P=0.04) was the only factor independently associated with the

Table 2 Univariate and multivariate Cox proportional hazard regression analysis to identify the independent factors associated with outcome in 52 patients with HBV decompensated cirrhosis

Baseline characteristics	95% confidence interval							
	Univariate analysis				Multivariate analysis			
	Hazard ratio	Lower	Upper	P value	Hazard ratio	Lower	Upper	P value
Age, years	0.93	0.87	0.99	0.035	0.907	0.817	1.006	0.07
Sex	1.24	0.33	4.64	0.74				
Diabetes mellitus	0.04	0.0	911.4	0.53				
ALT, (IU/L)	1.1	1.001	1.02	0.042	1.1	0.98	1.021	0,57
AST, (IU/L)	1.05	1.03	1.12	0.35				
HBV DNA, (IU/mL)	1	1	1	0.47				
Albumin, (g/dL)	1.06	0.47	2.38	0.88				
Hepatocellular carcinoma	2.88	0.58	14.4	0.19				
NAs before baseline	0.77	0.20	3.25	0.77				
GFR (MDRD), mL/min	0.98	0.95	1.02	0.22				
CTP score	0.95	0.60	1.51	0.83				
MELD score	1.05	0.91	1.22	0.51				
At 6 months								
GFR (MDRD), mL/min	1.004	0.97	1.04	0.81				
CTP score	1.48	0.86	2.53	0.15				
MELD score	1.25	1.02	1.54	0.034	1.125	0.843	1.502	0.422
ALT, (IU/L)	1.01	0.97	1.07	0.41				
AST, (IU/L)	1.22	1.1	1.55	0.24				
Changes between baseline and 6 months								
DCTP	2.51	1.07	5.88	0.035	1.8	0.71	4.56	0.21
DMELD	1.58	1.05	2.41	0.031	1.78	1.12	2.79	0.013

NAs, nucleos(t)ide analogues; CTP, child-pugh score; MELD, model for end stage of liver disease; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease; DMELD, changes in MELD score; DCTP, changes in CTP score; AST, asparate aminotransferase; ALT, alanine aminotransferase

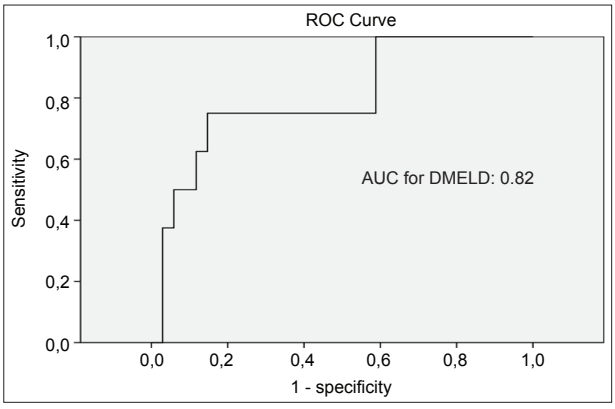

Figure 3 Area under the receiver operating characteristic curve (AUC) for prognostic scores in 52 patients with HBV decompensated cirrhosis under entecavir (ETV) or tenofovir (TDF). DMELD: changes in MELD score between baseline and after 6 months

outcome (Table 4). The discriminative ability of DCTP score was very good (AUC=0.81, 95% C.I.: 0.65-0.92) and DCTP of 0 was the best cut off point (sensitivity 60%, specificity 88%, PPV 0.43 and NPV 0.94) (Table 3, Fig. 4).

When only the 37 patients who were started on antiviral agents at baseline (19 under TDF and 18 under ETV) were evaluated, changes of MELD score from baseline to 6 months (DMELD) was again the only factor significantly associated with the outcome (HR: 1.8, 95% C.I. 1.19-4.5, P=0.03) with very good discriminative ability (AUC: 0.85, 95% C.I.: 0.67-0.95) and 0.42 as the best cut off point (sensitivity 80%, specificity 89%, PPV: 0.57 and NPV: 0.96). In the same subgroup of patients, the best cut off point for MELD score at 6 months was 15 with sensitivity 60%, specificity 90%, PPV: 0.50 and NPV: 0.93. When only the non-HCC naïve patients (n=32) were evaluated, the DCTP score, i.e. the changes of CTP score from baseline to 6 months, was the only independent factor associated with the outcome (HR: 3.86, 95% C.I. 1.19-12.5, P=0.024). In this subgroup of patients, the discriminative ability of DCTP score was excellent (AUC=0.96, 95% C.I.: 0.89-1.0) and DCTP of 0 was the best cut off point (sensitivity 100%, specificity 89%, PPV 0.76 and NPV 1.0).

Table 3 Prediction of outcome in HBV patients with decompensated cirrhosis

	Area under the ROC curve	Cut off point	Sensitivity (%)	Specificity (%)	PPV	NPV
DMELD score from baseline to 6 months (total group, n=52)	0.82	0.12	86	78	0.43	0.97
DCTP score from baseline to 6 months (non-HCC group, n=46)	0.81	0	60	88	0.43	0.94

ROC, receiver operating characteristic; PPV, positive predictive value; NPV, negative predictive value; CTP, child-pugh score; MELD, model for end stage of liver disease; HCC, hepatocellular cardinoma; DMELD, changes in MELD score; DCTP, changes in CTP score

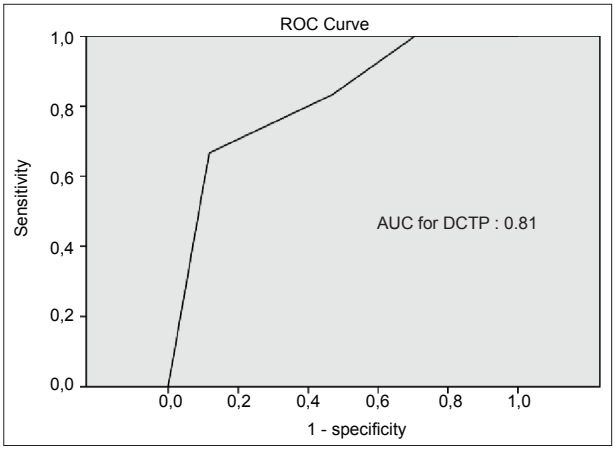

Figure 4 Area under the receiver operating characteristic curve (AUC) for prognostic scores in 46 non-HCC patients with HBV decompensated cirrhosis entecavir (ETV) or tenofovir (TDF). DCTP: changes in Child-Pugh score between baseline and after 6 months

Discussion

Present treatment guidelines advocate oral antivirals in patients with HBV-DeCi. ETV and TDF represent the currently recommended first-line NAs for this group of patients having potent antiviral activity with minimal or even null risk of resistance [3]. Both agents are considered to have similar virologic efficacy in patients with HBV-DeCi [9]. This has been clearly shown in the recent multicenter randomized study by Liaw *et al* [9], in which 112 patients with HBV-DeCi who received either TDF (n=45), emtricitabine (FTC)/TDF (n=45), or ETV (n=22) were evaluated. The authors found no difference in virologic efficacy with similar rates of patients with HBV DNA<400copies/mL at 3 months (51.2% vs 46.5% vs 50.0%, respectively) and 12 months (70.5% vs 87.8% vs 72.7%, respectively). In our retrospective study we also confirmed that both oral agents (ETV and TDF) had similar antiviral efficacy, since both ETV and TDF group of patients had undetectable HBV DNA at 12 months (using PCR with lower level of detection <45 IU/mL) and without virologic breakthrough during the follow up period. However, it should be mentioned that the HBV DNA levels at baseline were relatively low in both groups (median levels: 36,650 IU/mL vs. 5,920 IU/mL, P>0.05).

Nucleotide analogues (i.e. adefovir and less often TDF) have been associated with renal impairment, and this is of particular concern in HBV-DeCi patients. In the literature, there are few studies, in which ETV and TDF have been evaluated regarding their safety in HBV-DeCi patients. In the randomized study by Liaw *et al* [9], the 3 groups of patients (i.e. TDF, emtricitabine/TDF and ETV) had similar rates of renal dysfunction defined as increase in serum creatinine of ≥0.5mg/dL from baseline (8.9% vs 2.2% vs 4.5%, respectively, P>0.05) and hypophosphatemia defined as serum phosphorus <2.0 mg/dL (2.2% vs 4.4% vs 0%, P>0.05). In the same study [9], through 48 weeks, antiviral agents were well tolerated, since only 2 patients (one under TDF and one under emtricitabine/TDF) discontinued the treatment due to adverse events related to the study drug. More recently, Koklu *et al* [22] evaluated ETV and TDF in patients with HBV cirrhosis, including a subgroup of patients with HBV-DeCi (36 under ETV and 26 under TDF). The authors reported that both antiviral agents had comparable long-term safety and efficacy, but no specific details regarding HBV-DeCi patients were given [22]. In our study, we observed similar safety profile, since none of the patients discontinued the two drugs and no evidence of lactic acidosis was observed, although lactate levels were not monitored in all patients and most of our patients had relatively low MELD score. In addition, no difference in eGFR between the two groups was recorded (Fig. 1) and serum phosphate levels remained stable during the follow up period and with no significant difference between TDF and ETV groups of patients. Finally, none of the patients developed serum phosphate <2.0 mg/dL during the follow up period.

There is no doubt that patients with HBV-DeCi should be referred to be evaluated for LT [23]. In the last decade, however, the wider use of antiviral therapy in HBV-DeCi patients has often resulted in improvement of hepatic function [12-15] and even withdrawal from the waiting list for LT [16,17]. This improvement in the underlying hepatic reserve had been firstly recorded in the lamivudine era [16] and was confirmed more recently using the newer NAs [9,24]. In the study by Shim *et al* [24], 27 (49%) of 70 patients with HBV-DeCi who received ETV had reduction of CTP score ≥2 and the mean MELD score decreased from 11.1 at baseline to 8.8 at 12 months (mean reduction 2.3 points). Similarly, in the randomized study by Liaw *et al* [9], in the three subgroups of patients (TDF, FTC/TDF and ETV) the CTP score was improved by 2 or more points in 26%, 48% and 42%, respectively, while they had a median of 2 points reduction in MELD score at 12 months, compared to the baseline. In our cohort having similar severity of liver disease with the previous two studies [9,24] (mean CTP score at baseline: 8.1 vs 8.4 and 7, respectively), improvement in liver disease was also observed: 11 (21%) of the 52 patients had reduction in CTP score ≥2 at 12 months and 1.5 points was the mean reduction in the MELD score from baseline to 12 month. In fact, the reduction in CTP and MELD scores was

Table 4 Univariate and multivariate Cox proportional hazard regression analysis to identify the independent factors associated with outcome in 46 non-HCC patients with HBV decompensated cirrhosis

Baseline characteristics	95% confidence interval							
	Univariate analysis				Multivariate analysis			
	Hazard ratio	Lower	Upper	P value	Hazard ratio	Lower	Upper	P value
Age, years	0.93	0.86	1.007	0.074	0.91	0.83	1.013	0.087
Sex	1.77	0.39	7.94	0.45				
Diabetes mellitus	0.04	0.0	930.5	0.56				
ALT, (IU/L)	1.007	0.98	1.03	0.51				
AST, (IU/L)	1.22	1.15	1.41	0.36				
HBV DNA, (IU/mL)	1	1	1	0.57				
Albumin, (g/dL)	1.008	0.44	2.32	0.98				
NAs before baseline	1.25	0.28	5.63	0.77				
GFR (MDRD), mL/min	0.98	0.95	1.01	0.25				
CTP score	0.96	0.55	1.66	0.88				
MELD score	1.08	0.91	1.28	0.38				
At 6 months								
GFR (MDRD), mL/min	1.004	0.97	1.04	0.81				
CTP score	1.54	0.79	2.97	0.20				
MELD score	1.31	1.02	1.68	0.04	1.49	0.73	3.04	0.26
ALT, (IU/L)	1.005	0.94	1.07	0.89				
AST, (IU/L)	1.33	1.03	1.45	0.23				
Changes between baseline and 6 months								
DCTP	3.38	1.05	10.9	0.03	2.64	1.21	7.29	0.04
DMELD	1.45	0.86	2.45	0.14				

NAs, nucleos(t)ide analogues; CTP, child-pugh score; MELD, model for end stage of liver disease; GFR, glomerular filtration rate; MDRD, modificationo f diet in renal disease; DMELD, changes in MELD score; DCTP, changes in CTP score; AST, asparate aminotransferase; ALT, alanine aminotransferase

close to the improvement which was observed in the subgroup of TDF patients in the study of Liaw *et al* [9]. Interestingly, in the patients who underwent LT (n=6) the DMELD score between baseline and last follow up was 0.08, thus it was slightly increased during the follow up period.

However, the criteria and the most important parameters, which are associated with the survival of HBV-DeCi patients under antiviral agents, have not been elucidated. Studies using lamivudine monotherapy in HBV-DeCi patients have shown that the most important independent pre-treatment parameters prognostically associated with the survival are serum bilirubin, creatinine and high HBV-DNA levels [16]. Although it had been shown that the severity of liver disease at the initiation of antiviral therapy and not the achievement of early virological response has greater impact for the early survival [16], it was not clear if these results from the lamivudine era were still valid considering the current availability of more potent anti-HBV agents and more sensitive HBV-DNA assays.

A recent study [25] including 45 HBV-DeCi patients under ETV and 41 under lamivudine found that although HBV DNA suppression (using sensitive PCR technique) was more potent and with less frequent development of viral breakthrough in the ETV group than the lamivudine group, 6-month mortality rates did not differ between the two groups [25]. In the same study [25], CTP score at baseline and MELD score at 3 months of antiviral treatment were the only factors significantly associated with mortality at 6 months. However, separate analysis for ETV alone was not reported and ETV was compared to lamivudine and not TDF [25]. In our retrospective study, we confirmed the findings by Hyaun *et al* [25], that HBV DNA levels at baseline were not associated with the patients' outcome (death or LT) in the total cohort and in the subgroup of naïve patients. Additionally, in the total group of patients, the changes of MELD score (DMELD) from baseline to 6 months was the only factor independently associated with the survival without LT (HR; 1.78, 95% C.I.: 1.12-2.79, P=0.013)(Table 2). This finding was confirmed in the subgroup of naïve patients who were started on antiviral agents at baseline (19 under TDF and 18 under ETV), in which the DMELD score was also the only independent prognostic factor of the outcome (HR: 1.8, 95% C.I. 1.19-4.5, P=0.03). In both cases, DMELD score had very good discriminative ability [AUC: 0.82 (95% C.I. 0.67-0.92) and 0.85 (95% C.I. 0.67-0.95, respectively], with best cut-off points 0.12 and 0.42, respectively. Interestingly,

when only the non-HCC patients were evaluated, changes of CTP score (DCTP) from baseline to 6 months (HR: 2.64, 95% C.I. 1.21-7.29, P=0.015) was the only factor independently associated with the outcome, and this was confirmed in the subgroup of non-HCC naïve patients (HR: 3.86, 95% C.I. 1.19-12.5, P=0.024). In both cases, the DCTP of 0 was the best cut-off point with very good discriminative ability. Finally, in contrast to previous studies [9,24], none of our patients died or underwent to LT during the first 6 months of follow up. In fact, our findings were similar to those by Lian *et al* [26], in which 60 patients with HBV-DeCi under lamivudine plus adefovir and 60 patients with HBV-DeCi under ETV were evaluated. The authors reported no death or LT during the first 6 months. However, no clear explanation could be given regarding these conflicting literature data.

We acknowledge that our study has some limitations including its retrospective nature. In addition, MELD and CTP scores were not available at 3 months, and thus, were not able to confirm the findings of Hyun *et al* [25] regarding the prognostic impact of MELD score at 3 months for early mortality. However, our patients, compared to those in the study by Hyun *et al* [25], had less severe liver function at baseline (mean MELD score 12.1 vs 16.9) and none of the patients died during the first 6 months.

In conclusion, in our cohort of patients with HBV-DeCi, both antivirals (ETV and TDF) were well tolerated; none of the patients discontinued therapy, while eGFRs and phosphate levels were not different between TDF and ETV groups during the total follow up period. In addition, our patients had excellent virological response without viral breakthrough and with stabilization or improvement in severity of liver disease. Finally, regarding the prognostic factors associated with the outcome of HBV-DeCi patients under ETV or TDF, practically, a worsening of MELD score and CTP score (in non-HCC patients) from baseline to 6 months had very good performance and they were associated with poor LT-free survival making these indexes useful prognostic markers in HBV-DeCi patients.

Summary Box

What is already known:

- The use of antiviral therapy in patients with HBV decompensated cirrhosis (HBV-DeCi) has often resulted in improvement of hepatic function and even withdrawal from the waiting list for liver transplantation (LT)
- Although the nephrotoxic potential is considered to be higher for nucleotide analogues, there are still concerns about the potential nephrotoxicity of tenofovir (TDF)
- Recently, Child Pugh (CTP) score at baseline and MELD score at 3 months of antiviral treatment were the only factors significantly associated with mortality. However, comparison between entecavir (ETV) vs TDF has not been reported on this topic

What the new findings are:

- TDF and ETV appear to have similar renal safety profile in HBV-DeCi patients
- In patients with HBV-DeCi under ETV or TDF, the change in MELD (DMELD) score between baseline and after 6 months was independently associated with the outcome
- In patients with HBV-DeCi without hepatocellular carcinoma (HCC) under ETV or TDF, the change in CTP score between baseline and after 6 months was independently associated with the outcome

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