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ORIGINAL ARTICLE

New nucleos(t)ide analogue monoprophylaxis after cessation of hepatitis B immunoglobulin is effective against hepatitis B recurrence

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Conflicts of interest
Evangelos Cholongitas: invited speaker for BMS, Gilead, Novartis; Ioannis Goulis, Nikolaos Antoniadis, Ioannis Fouzas, George Imvrios, Vasilios Papanikolaou, Evangelos Akriviadis: nothing to disclose.

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Summary

New nucleos(t)ide agents (NAs) [entecavir (ETV) and tenofovir (TDF)] have made hepatitis B immunoglobulin (HBIG)-sparing protocols an attractive approach against hepatitis B virus (HBV) recurrence after liver transplantation (LT). Twenty-eight patients transplanted for HBV cirrhosis in our centre were prospectively evaluated. After LT, each patient received HBIG (1000 IU IM/day for 7 days and then monthly for 6 months) plus ETV or TDF and then continued with ETV or TDF monoprophylaxis. All patients had undetectable HBV DNA at the time of LT, and they were followed up with laboratory tests including glomerular filtration rate (GFR) after LT. All patients (11 under ETV and 17 under TDF) remained HBsAg/HBV DNA negative during the follow-up period [median: 21 (range 9–43) months]. GFR was not different between TDF and ETV groups of patients at 6 and 12 months and last follow-up (P value >0.05 for all comparisons). The two groups of patients were similar regarding their ratio of maximum rate of tubular phosphate reabsorption to the GFR (TmP/GFR). In conclusion, in this prospective study, we showed for the first time that maintenance therapy with ETV or TDF monoprophylaxis after 6 months of low-dose HBIG plus ETV or TDF after LT is highly effective and safe.

Introduction

The improvement in the treatment of patients with hepatitis B virus (HBV) over the last years, with the development of effective, well-tolerated and relatively safe oral antiviral agents [nucleos(t)ide analogues (NAs)], has offered the opportunity for successful management of HBV chronic liver disease [1]. However, chronic HBV infection (CHB) is still associated with increased morbidity and mortality. Currently, it is estimated that more than half a million people die every year due to complications related to liver decompensation, and HBV-decompensated cirrhosis is a frequent indication for liver transplantation (LT) in the Far East and the Mediterranean countries [2].

The third-generation NAs, entecavir (ETV) and tenofovir (TDF), are potent antiviral agents with high genetic barrier and are currently recommended as the first-line NAs for the treatment of patients with CHB. Both ETV and TDF achieve complete viral suppression in the vast majority of patients and reduce but not eliminate the incidence

of hepatocellular carcinoma (HCC) [3,4]. The latter is expected to increase during the next years because the patients who have already CHB cannot benefit from the nationwide vaccination programmes [5]. HCC is currently the most common cause of LT in patients with CHB [5].

Post-transplant HBV recurrence was almost universal in the era of no immunoprophylaxis, particularly in those with detectable HBV DNA at the time of LT [3]. Recurrent HBV had usually an aggressive course leading to graft loss [6]. Antiviral prophylaxis against HBV recurrence after LT has evolved over the last years with the introduction of combination of hepatitis B immunoglobulin (HBIG) and NAs [7]. The former significantly decreased the rate of post-LT HBV recurrence, but it has several limitations including considerable cost, availability and the need for parenteral administration. The new NAs (ETV and TDF) are currently used in the post-transplant period in many transplant centres, instead of lamivudine, in an effort to decrease the need for the expensive HBIG preparations and the post-transplant HBV recurrence rate and to improve prognosis after LT. In our recently published systematic review [7], the patients under HBIG and lamivudine developed HBV recurrence significantly more frequently, compared to patients under HBIG and ETV or TDF [115/1889 or 6.1% vs. 3/303 or 1.0%, $P < 0.001$]. Given the fact that most patients have undetectable HBV DNA at the time of LT, one attractive strategy would be the use of HBIG for a limited period after LT followed by long-term new NA(s) therapy alone [7]. In recent studies, this antiviral prophylactic approach has been applied [7]. However, in these studies, HBIG has been given in relative high dosages and/or for several months or years before its withdrawal, while dual NA(s) prophylaxis (i.e. nucleoside + nucleotide analogue) has been used after HBIG discontinuation [8–11].

The aim of the present prospective study was to evaluate for the first time the safety and efficacy of maintenance therapy with ETV or TDF monoprophylaxis after a short course with low-dose HBIG plus ETV or TDF after LT.

Methods

We enrolled all consecutive adult patients transplanted with deceased liver graft for HBV cirrhosis from September 2010 to July 2013, and they were prospectively studied until April 2014, when the clinical status was evaluated. These patients were HBsAg positive, HBeAg negative/anti-HBeAg positive and anti-HBcore positive at the time of LT [eight patients had genotype D, but in the other patients, no genotype determination was performed]. There were no specific exclusion criteria including the co-infection with hepatitis D or hepatitis C viruses. All patients signed a consent form. In each patient, data regarding demographics, clinical and laboratory data, antiviral therapy pre- and post-LT, adverse effect of antiviral therapy, immunosuppression regimen, recurrence of HBV infection and survival data were extracted from the medical records.

All included patients were followed up with renal function assessment, calcium, phosphate and liver function tests daily during the first 10–15 days after LT, biweekly or weekly for the first 2–3 months and then every 1–3 months or at shorter intervals according to the clinical course of liver transplant recipients. Assessment of renal function was based on estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) and chronic kidney disease epidemiology collaboration (CKD-EPI) formulae [12,13]. In addition, at 12 months after LT, we evaluated the ratio of 'tubular maximum for phosphate corrected for GFR' (TmP/GFR; normal values: 2.8–4.4 mg/dl), as a more accurate indicator of renal phosphate handling irrespectively of plasma phosphate and GFR [14].

Hepatitis B virus serum markers (HBsAg, anti-HBs, HBeAg, anti-HBe) were evaluated every 7 days for the 1st month and then every 1–3 months until the end of follow-up using the same standard commercial assays. HBV DNA was assessed 1–6 months before LT, at 15th and 30th day after operation and then at 3–6 months intervals using the same standardized real-time PCR (COBAS TaqMan, Roche Molecular Systems) with lower level of detection 6 IU/ml. Surveillance for HCC recurrence included alpha-fetoprotein and computer tomography and/or magnetic resonance imaging scanning at 1st month, 6th month after operation and yearly thereafter. The study was approved from the local ethical committee and performed in accordance with the Declaration of Helsinki.

Immunosuppression protocol

The standard immunosuppression protocol at our centre consisted of combination of calcineurin inhibitor (CNIs) (cyclosporine and less frequently tacrolimus), mycophenolate mofetil and methylprednisolone therapy. CNI was administered at the first day after LT intravenously or orally with dose adjustments according to therapeutic drug levels and renal function. In patients with HCC pre-LT or renal dysfunction after LT, everolimus was used instead of a calcineurin inhibitor after the 1st month postoperatively. Methylprednisolone was initiated with a 1-gm intravenous bolus immediately after the reperfusion of the hepatic graft and then tapered to 200 mg/day (day 1), 160 mg/day (day 2), 120 mg/day (day 3), 80 mg/day (day 4), 40 mg/day (day 5) and 20 mg/day (day 6) and was discontinued 3–6 months after LT.

HBIG and NA protocol

After LT, each patient received combination of prophylaxis with HBIG plus ETV or TDF. All patients were under ETV

or TDF before LT and the same NA was continued after LT. HBIG was given at low dosage, that is, 1000 IU intravenously intra-operatively (anhepatic phase) and daily for the first week and then 1000 IU/month intramuscularly for 6 months post-LT. At 6 months, HBIG was withdrawn and the patients continued with ETV or TDF monoprophylaxis. The dose of NA was adjusted to renal function according to the current guidelines.

Study end point

The clinical status (dead or alive) of the patients was assessed at the end of follow-up, while HBV recurrence was defined as the reappearance of detectable serum HBsAg and/or HBV DNA during the follow-up period.

Statistical analysis

All data were analysed using the statistical package SPSS (version 19.0 SPSS Inc, Chicago, IL, USA). The chi-squared test was used for comparing qualitative variables, and Student's *t*-test and Mann–Whitney *U*-test were used for comparing quantitative continuous variables. Paired *t*-test or Wilcoxon matched-paired test was used for the comparisons between the eGFRs and serum phosphate at different time points. Quantitative variables which were normally distributed were expressed as mean values ± one standard deviation (SD), and those non-normally distributed were expressed as median values (range). Significance testing was two-sided and set at $P < 0.05$.

Results

Demographic characteristics

A total of 28 liver transplantations were performed for HBV-decompensated cirrhosis during the study period at our centre. None of the patients received liver graft from anti-HBcore-positive donor. The baseline characteristics of the patients are presented in Table 1. There were 20 men with median age 53 (range: 30–64) years. All patients had undetectable HBV DNA at the time of LT. Eight patients had HDV co-infection and none HCV/HBV co-infection. Fourteen patients had HCC before LT (11 within Milan criteria); eight (57%) of them had received locoregional therapies (chemoembolization or radiofrequency ablation). At the time of LT, the mean (±SD) MELD score was 16 ± 5 (Table 1). Six (21%) of the 28 patients had been converted from lamivudine plus adefovir to TDF at least 8 months prior to LT, and all patients were under antiviral therapy with new NA(s) (i.e. ETV or TDF) at least 6 months before operation.

Table 1. Characteristics of the 28 recipients under new nucleos(t)ide analogue (NA) prophylaxis after LT for prevention of hepatitis B recurrence.

Variable	
Age, mean ± SD (years)	53 ± 10
Sex, male, *n* (%)	20 (71)
MELD at LT, mean ± SD	16 ± 5
Detectable HBV DNA pre-LT, *n* (%)	0 (0)
Hepatitis delta positivity pre-LT, *n* (%)	8 (28)
Pre-LT HCC n, (%)	14 (50)
Post-LT HCC recurrence, *n* (%) (among those with pre-LT HCC)	1 (7)
Estimated glomerular filtration rate (MDRD formula) at the time of LT, ml/min	63 ± 18
Time of follow-up after LT, median (range), months	18 (8–40)
Antiviral prophylaxis, *n* (%)	
Entecavir	11 (39)
Tenofovir	17 (61)
Immunosuppression, *n* (%)	
CNIs + MMF	17 (61)
CNIs + everolimus	11 (39)
Death during the follow-up, *n* (%)	2 (7)

LT, liver transplantation; HCC, hepatocellular carcinoma; MDRD, modification of diet in renal disease; CNI, calcineurin inhibitor.

Antiviral prophylaxis and hepatitis B recurrence

Eleven patients were under ETV (group 1) and 17 under TDF (group 2) at the time of LT, and the same antiviral therapy was continued after LT. All patients remained HBsAg-negative and with undetectable HBV DNA during the follow-up period [21 (range 9–43) months]. After HBIG discontinuation at 6 months, the median levels of anti-HBs at 6 months, 12 months and last follow-up were gradually decreased (360 IU/ml vs. 157 IU/ml vs. 5.8 IU/ml, respectively) and seven (25%) had undetectable anti-HBs levels at the last follow-up. Five (18%) of the 28 patients underwent liver biopsy at a mean time of 14 ± 3 months after LT with no evidence of HBV recurrence on histological examination of the liver specimen. HCC recurrence was detected in only one (7%) of the 14 patients with HCC before LT. This patient had HCC within Milan criteria before LT. Its recurrence was confirmed based on laboratory and radiographic findings 30 months after LT. The patient was commenced on sorafenib 400 mg per day, and he remained in stable clinical condition without evidence of HBV recurrence under TDF during the follow-up period. All patients were alive and continued to be followed at the time of analysis except from two patient who died due to liver graft loss 14 and 18 months after LT, respectively. The first patient, a 35-year-old woman, under TDF, died from acute cellular rejection (confirmed by liver biopsy) attributable to voluntary discontinuation of immunosuppressive therapy. Although the immunosuppressive

therapy was re-instituted and the patient received intense antirejection therapy, the liver graft function was never recovered. The second patient, a 62-year-old man, under ETV, died from liver failure with concomitant hepatic abscess secondary to hepatic artery thrombosis. None of these two patients had evidence of HBV recurrence based on HBsAg or HBV DNA during their clinical course.

Safety profile and renal function

The antiviral prophylaxis was well tolerated, and none of the patients discontinued their NAs. No symptoms, signs or laboratory findings were judged to be related to ETV or TDF administration including the two patients who died from liver graft loss.

In the total cohort, eGFRs based on MDRD formula at 6 months, 12 months and last follow-up were 59 ± 22, 63 ± 30 ml/min and 62 ± 23 ml/min, respectively ($P > 0.05$ for all comparisons). The patients under ETV (group 1), compared to those under TDF (group 2), had similar clinical characteristics at baseline (Table 2). eGFRs were not different between TDF and ETV groups of patients at 6 months (55 ± 14 vs. 68 ± 30 ml/min), 12 months (57 ± 13 vs. 68 ± 28 ml/min) and last follow-up (56 ± 15 vs. 66 ± 31 ml/min) (P value >0.05 for all comparisons) (Fig. 1). These results were confirmed when eGFRs were estimated using the CKD-EPI formula (data not showed). Three patients under TDF (17%) and two (18%) under ETV required a reduction to alternate-day dosing at some point during the follow-up period because eGFR was <50 ml/min. Finally, the two groups of patients were similar at 6 months, 12 months and last follow-up regarding their serum phosphate (Fig. 2) as well as TmP/GFR at 12 months (2.9 vs. 3.4 mg/dl, respectively, $P = 0.43$). Serum phosphate levels remained normal (≥2 mg/dl) in all patients, and none of them required antiviral modification due to low levels of serum phosphate.

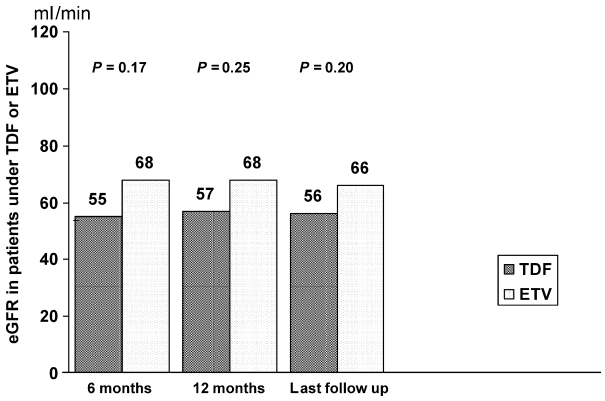

Figure 1 Evolution of glomerular filtration rates in the group of patients under entecavir (ETV) and tenofovir (TDF) as calculated by modification of diet in renal disease (MDRD) formula.

Table 2. Clinical characteristics of tenofovir and entecavir groups of patients given as prophylaxis after LT for prevention of hepatitis B recurrence.

Variable (unit)	Patients under tenofovir (n = 17)	Patients under entecavir (n = 11)	P
Age, mean ± SD (years)	53 ± 10	53 ± 8	0.97
Sex, male, n (%)	14 (82)	6 (55)	0.20
MELD at LT, mean ± SD	16 ± 3	15 ± 4	0.84
Detectable HBV DNA pre-LT	0 (0)	0 (0)	–
Hepatitis delta positivity pre-LT, n (%)	4 (24)	4 (36)	0.36
Pre-LT HCC, n (%)	9 (53)	5 (45)	0.88
Post-LT HCC recurrence, n (%) (among those with pre-LT HCC)	1 (11)	0 (0)	0.23
After LT			
Diabetes mellitus, n (%)	3 (17)	3 (27)	0.23
Arterial hypertension, n (%)	3 (17)	2 (18)	0.82
Immunosuppression, n (%)			
CNIs + MMF	8 (47)	9 (82)	0.09
CNIs + everolimus	9 (53)	2 (18)	
Time of follow-up after LT, median (range), months	19 (9–40)	16 (8–37)	0.41

LT, liver transplantation; HCC, hepatocellular carcinoma; CNI, calcineurin inhibitor.

Discussion

Currently, combination of HBIG and NA(s) is the most commonly used antiviral prophylaxis against HBV recurrence after LT. However, the optimal antiviral protocol remains uncertain, particularly regarding HBIG dosage and duration due to lack of randomized comparative studies.

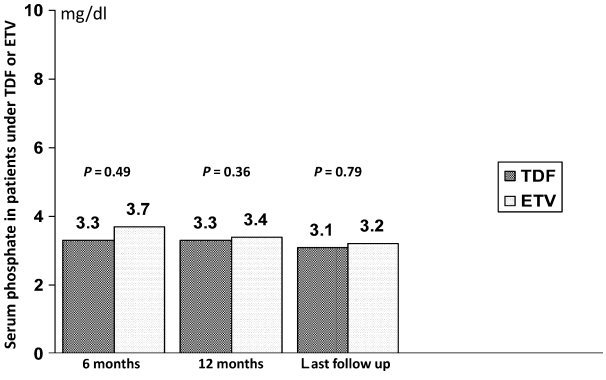

Figure 2 Evolution of serum phosphate levels in the group of patients under entecavir (ETV) and tenofovir (TDF).

Nevertheless, as most of the patients have undetectable HBV DNA levels at the time of LT and thus are at low risk of HBV recurrence, several transplant centres have adopted the use of HBIG for a finite period after LT followed by long-term NA therapy [7]. This strategy of HBIG withdrawal had been used firstly with lamivudine, but the final long-term results were disappointing, as up to 20% of the patients developed HBV recurrence [15,16]. The newer high genetic barrier NAs (ETV and TDF) seem to be a better choice allowing earlier and safer discontinuation of HBIG. Indeed, in our systematic review [7], we found that the use of ETV- or TDF-based prophylaxis after HBIG discontinuation has similar efficacy to the long-term combination of HBIG and lamivudine (3.9% vs. 6.1%, $P = 0.52$).

In the literature, few studies (published as full papers and including more than ten patients) have assessed the effectiveness of prophylactic protocol using new NA(s)-based antiviral prophylaxis with limited duration of HBIG (Table 3). Saab *et al.* [8] found low rates of HBV recurrence giving dual antiviral prophylaxis after HBIG discontinuation (various protocols of HBIG at different study periods were used). Teperman *et al.* [9] found no HBV recurrence in 18 patients who had received HBIG plus NA(s) for a median time of 3.4 years after LT (no further details were provided regarding HBIG protocol), and then, they had been randomized to continue with TDF plus emtricitabine, while in the study by Wesdorp *et al.* [11], 2 (11.8%) of the 17 patients experienced HBV recurrence using the same oral antiviral prophylaxis (TDF plus emtricitabine) after HBIG withdrawal. The latter had been given in high dosage (10 000 IU) and for more than 6 months after LT. In the study by Stravitz *et al.* [17], 21 patients discontinued HBIG at a mean time of 6.6 years after LT and they continued with the combination of TDF plus emtricitabine, while in the study by Tanaka *et al.* [18], 24 patients received low dosage of HBIG plus TDF ± lavivudine for 12 months and then only TDF ± lavivudine. In both studies, negligible rates of HBV recurrence were reported. Finally, in our previous published study [10], 1 (4.1%) of the 24 patients developed HBV recurrence under ETV- or TDF-based prophylaxis after withdrawal of high-dose HBIG given for at least 12 months after LT (Table 3). In contrast to the previous published studies, in which higher dosage of HBIG for longer period and/or combination of NAs were given before or after HBIG discontinuation (Table 3), the present study is the first one in which ETV or TDF monoprophylaxis was used as long-term prophylaxis (after short course with low-dose HBIG plus ETV or TDF for only 6 months) in consecutive patients without exclusion criteria. Under this simple antiviral protocol, none of the patients had HBV recurrence (HBsAg negativity and HBV DNA undetectability) after a median of 21-month follow-up. Achievement of HBsAg negativity may be related with the binding of HBIG with circulating viral particles preventing infection of hepatocytes and decreasing HBsAg secretion. In fact, combination of HBIG plus NA(s) (the latter given to suppress viral replication) seems to represent a more reasonable choice during the first post-LT

Table 3. Studies published as full papers for prevention of hepatitis B virus (HBV) recurrence under new nucleos(t)ide analogues (entecavir or tenofovir) after discontinuation of HBIG in patients transplanted for HBV-related liver disease.

Study 1st author, year (Ref no.)	Patients, *n*	Post-LT HBIG: [Anhepatic]/[1st week]/[1st month]	Time of HBIG withdrawal after LT	ETV- and TDF-based antiviral prophylaxis	Follow-up, months	HBV recurrence, *n* (%)
Saab, 2011 [8]	61 (but no data for ETV/TDF)	Different protocol of HBIG at different periods	>12 months	Nucleoside + nucleotide analogue	15	2 (3.3)
Cholongitas, 2012 [10]	24	[10 000 IV]/[10 000/day IV]/ 2000/month IM	>12 months	Nucleoside ± nucleotide	24	1 (4.1)
Stravitz, 2012 [17]	21	[10 000 IV]/[1500/day IV]/ based on anti-HBs IM	>6 months (mean 6.6 years)	TDF+emtricitabine	31.1	1 (4.7)
Teperman, 2013 [9]	18 (in the 1st arm of the randomized study)	No data	>9 months (median time 3.4 years after LT)	Tenofovir+ emtricitabine	18	0
Wesdorp, 2013 [11]	17	[10 000 IV]/[10 000/day IV]/ 10 000/month	>6 months	Tenofovir + emtricitabine	26	2 (11.8)
Tanaka, 2014 [18]	24	[2000 IV]/[2000/day IV or IM]/ [2000/week/]2000 IM/month for 12 months	12 months	TDF (±lamivudine)	29.1	0
Present study	28	[1000 IV]/[1000/day IV]/1000/ month IM for 6 months	6 months	ETV or TDF	21	0 (0)

HBIG, hepatitis B immunoglobulin; LT, liver transplantation; ETV, entecavir; TDF, tenofovir.

period. It should be mentioned that our patients had undetectable HBV DNA at the time of LT. Nevertheless, it is true that the introduction of new NA(s) has led to successful suppression and achievement of undetectability HBV DNA in the vast majority of HBV patients in the waiting list for LT, while in cases of prophylaxis failure, there are still options to successfully suppress HBV replication and prevent graft loss.

In the era of potent high genetic barrier NAs (ETV and TDF) and considering the limitations of HBIG, recent antiviral protocols against HBV recurrence have evolved towards the use of less HBIG or even HBIG-free prophylaxis [19]. The latter has been evaluated in our recent systematic review [7], showing that post-LT HBV recurrence was observed significantly more frequently in the patients under new NA(s) HBIG-free prophylaxis, compared to those under new NA(s) after HBIG discontinuation, if the definition of HBV recurrence was based on HBsAg positivity [26% vs. 3.9%, $P < 0.0001$]. However, the rates of HBV recurrence were similar between the two groups if the definition of HBV recurrence was based on HBV DNA detectability (0.9% vs. 0%, $P = 0.35$) [7]. As the clinical significance of HBsAg seropositivity in HBV transplant recipients under immunosuppression remains unclear, we believe that antiviral prophylaxis using new NA(s) after discontinuation of low dosage HBIG for short term after LT seems to be a reasonable and cost-effective approach to ensure HBsAg negativity and HBV DNA undetectability in the liver transplant recipients. However, it should be mentioned that in HBV transplant recipients on NA(s) prophylaxis, close monitoring is needed for evaluation of adherence and prompt diagnosis of HBV recurrence.

In the pre-LT setting, renal toxicity is considered a concern for NA, particularly adefovir [20,21]. In the literature, only few studies have evaluated the impact of NAs on renal function in the post-LT setting. In our previous study [10], we found that MDRD-based eGFR and serum phosphate levels were not significantly different between the group of patients under nucleotide analogues (adefovir or TDF), compared to those under ETV. In the present study, evaluation of eGFR was based for the first time on both MDRD and CKD-EPI formulae, and we confirmed that eGFRs were not different between ETV and TDF groups of liver transplant recipients at 6 months, 12 months and last follow-up (Fig. 1). In addition, the two groups of patients had similar serum phosphate during the study period (Fig. 2). Regarding TmP/GFR, it is considered a convenient way to evaluate renal phosphate transport for the assessment of renal tubular disorders, such as Fanconi's syndrome [14]. This sensitive index has been evaluated in CHB patients under NAs, but never before in the post-LT setting. In our study, we found no difference in TmP/GFR ratio between ETV and TDF groups of liver transplant recipients. It is true that our patients had relatively low eGFRs at 6 and 12 months after LT, although 'nephroprotective' immunosuppressive regimes (CNIs plus MMF or everolimus) had been used. The precise impact of ETV/TDF administration on this finding cannot be determined. Nevertheless, careful renal function monitoring is needed in all LT recipients due to the use of calcineurin inhibitors and the frequent coexistence of diabetes mellitus and arterial hypertension [21].

Our study has some limitations including the lack of randomization and the relative short follow-up of a small cohort. In addition, all patients were at low risk of HBV recurrence as they had negative HBV DNA at the time of LT, but in the era of new NAs, the vast majority of the patients are transplanted with undetectable HBV DNA. In conclusion, in this prospective single-centre study including all consecutive patients without exclusion criteria, we showed for the first time that ETV or TDF monoprophylaxis (after short course with low-dose HBIG plus ETV or TDF for only 6 months postoperatively) seems to be effective against HBV recurrence after LT. In addition, we found that both ETV and TDF have similar renal safety profile in the LT setting regarding GFR (based on MDRD and CKD-EPI) and tubular dysfunction. The latter was based on assessment of serum phosphate and (for the first time in the LT setting) TmP/GFR. However, the small number of patients prevents from reliable suggestions and further larger prospective studies with longer follow-up are needed for final conclusions.

Authorship

EC, IG, NA and IF: performed the research. EC, GI, VP and EA: wrote the paper. EC: analysed the data.

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