Tenofovir alafenamide prophylaxis post-liver transplantation: a real-world study in patients with chronic kidney disease

E. Sinakos[1], P. Panas[1], N. Fragkou[1], N. Antoniadis[2], G. Katsanos[2], E. Tsakni[2], T. Oikonomou[1], A. Notopoulos[3], G. Tsoulfas[2], I. Goulis[1], E. Akriviadis[1]

(1) 4th Medical Department, Hippokratio Hospital, Aristotle University of Thessaloniki, Greece; (2) Department of Transplant Surgery, Hippokratio Hospital, Aristotle University of Thessaloniki, Greece; (3) Department of Nuclear Medicine, Hippokratio Hospital, Thessaloniki, Greece.

Abstract

Background & aims: **Tenofovir alafenamide fumarate (TAF) was shown equally efficacious in suppressing hepatitis B virus (HBV) but with less renal toxicity than tenofovir disoproxil fumarate (TDF). The aim of this real-world study was to evaluate renal function in post-liver transplantation (LT) patients that changed TDF with TAF.**

Methods: **The TAF group (n=17) included patients who switched to TAF due to low (<60 ml/min/1.73m^2) Glomerular Filtration Rate (GFR). The control group included patients that remained on TDF (n=30), although some (n= 14) had chronic kidney disease (CKD) (TDF-CKD group). GFR was assessed using: i) MDRD-6 variable; ii) CKD-EPI formula; iii) radionuclide technique (rGFR).**

Results: **There were no significant differences between the two groups except for the presence of diabetes and follow-up period, which were more common and shorter, respectively, in the TAF group (35% vs. 10%, p=0.03; 13.7 vs. 35.5 months, p<0.001). At the end of follow-up there were no significant changes in renal function between the TAF and the TDF group or TDF-CKD group, although the numerical change in rGFR in the latter comparison was greater in the TAF group (ΔrGFR 3 vs. -2.14 ml/min, p=0.26). The use of everolimus was associated with improvement in renal function (ΔrGFR 2 vs. -7.75 ml/min, p=0.06 [TAF vs. TDF group]; 2 vs. -12 ml/min, p=0.01 [TAF vs. TDF-CKD group]). There were no TAF-related side effects or cases of HBV recurrence.**

Conclusion: **Conversion to TAF in post-LT patients who develop CKD does not lead to improvement of kidney function after a period of one year.** (Acta gastroenterol. belg., **2022,** 85, **1-7**).

Keywords: Tenofovir alafenamide, liver transplantation, chronic kidney disease, prophylaxis, hepatitis B.

Introduction

The continuous use of nucleses(t)ide analogues (NA) is currently recommended to prevent Hepatitis B Virus (HBV) re-infection of the graft in patients that have undergone liver transplantation (LT) for this indication (1). Potent antiviral drugs are preferred in this setting, typically tenofovir disoproxil fumarate (TDF) or entecavir (ETV). These drugs are generally safe, although mild adverse events have been reported with their use. Tenofovir alafenamide fumarate (TAF) is a newer antiviral drug that is actually a prodrug of TDF. It has shown non-inferiority to TDF in suppressing HBV also having an improved renal and bone safety (2). However, the changes in renal function in the registration trials of TAF were only minimal without clear clinical significance (3).

TDF is considered to have a higher nephrotoxic potential as compared with ETV. Fanconi syndrome, but also chronic tubular damage and decline of Glomerular Filtration Rate (GFR) have been associated with the prolonged use of TDF, mainly in patients with Human Immunodeficiency Virus (HIV) infection (4,5). Real-world evidence showed that TDF is associated with reductions in eGFR as compared to ETV or telbivudine in patients with HBV infection, although it seems that it does not increase the risk of chronic kidney disease (CKD) (6,7). It is generally approved that renal damage of clinical significance caused by TDF is uncommon in the short-/mid-term and that it occurs more frequently when predisposing factors for kidney injury are also present (8).

Liver transplant recipients are susceptible to CKD mainly due to calcineurin inhibitor (CNI) immuno-suppression. It has been shown that chronic renal failure, as defined by a GFR below 30 ml/min/1.73m^2, occurs in 18% of liver transplant recipients at year 5 after LT (9). Strategies to prevent CKD include minimization of CNI use and adequate control of concomitant metabolic comorbidities. There are no specific guidelines regarding the use of NA in liver transplant recipients that develop CKD.

Data on the use of TAF in liver transplant recipients are extremely limited. Recently a trend toward improvement in renal function was shown when switching from TDF to TAF for HBV prophylaxis in liver transplant recipients (10-12). These studies had small sample size and variable study design hence emphasizing the need for additional data to confirm the beneficial effect of TAF in transplant recipients.

The aim of this real-world study was to evaluate the changes in renal function in post-LT patients with CKD that have switched from TDF to TAF for HBV prophylaxis.

Correspondence to: Emmanouil Sinakos, Hippokratio Hospital, 49, Konstantinoupoleos Str, Thessaloniki, Greece, 54642. Phone: +30 6944912668. Email: esinakos@auth.gr

Submission date: 31/07/2021
Acceptance date: 29/11/2021

Patients and Methods

Study population and design

All liver transplant recipients due to HBV infection in our transplant center who received either TDF continuously or TAF after a period of TDF therapy were included in this study. Liver transplant recipients in our center (Hippokratio Hospital, Aristotle University of Thessaloniki, Greece) receive a combination of a NA (ETV or TDF) with Hepatitis B Immunoglobulin (HBIG), typically for 6 months post LT. After this time period, HBIG is discontinued and patients remain on oral antiviral therapy. Indication for switching to TAF is: i) GFR <60ml/min/1.73m^2, ii) serum phosphorus levels <2.5 mg/dl and iii) dual-energy x-ray absorptiometry (DEXA) derived T-score <-2.5 SD. These indications correspond to the reimbursement policy of the Greek National Insurance Organization (EOPYY), which started to reimburse TAF in January 2018 but only under restricted circumstances.

Exclusion criteria included co-infection with hepatitis C or human immunodeficiency virus, positive serum HBV DNA, use of hemodialysis and follow up period less than six months after conversion to TAF.

Demographic data and post-transplant comorbidities including arterial hypertension and diabetes mellitus were recorded. Chart review for clinical and laboratory follow-up was performed in a retrospective/prospective manner between January 2019 and March 2020 based on routine visits, typically held every three months. Estimation of GFR with radionuclide techniques (rGFR) was usually performed every two years or whenever clinically indicated. The commencement and conclusion of the follow-up period in every case was associated with a concurrent rGFR measurement. The immunosuppressive regimen and the relevant drug levels were also recorded. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

The main outcome of this study was the change in renal function after switching to TAF. Secondary outcomes included recurrence of serum HBsAg, and graft survival.

Assessment of renal function

Conventional commercial assays were used to calculate serum creatinine (sCr) and serum phosphorus levels. Estimated GFR (eGFR) was assessed using the i) MDRD-6 variable (Modification of Diet in Renal Disease) and ii) the CKD-EPI (Chronic kidney disease-epidemiology) sCr-based formula (13,14). rGFR measurement was performed using either ^{51}Chromium-EDTA or ^{99m}Technetium-DTPA by sampling blood, after intravenous injection of tracer over 1-2 minutes, at 2, 4, and 6 hours. ^{51}Chromium-EDTA was exclusively used until September 2019 when it became no more available in our center and hence was replaced by ^{99m}Technetium-DTPA. rGFR was calculated using the slope-intercept technique, correcting for body surface area and the fast exponential curve as recommended by the British Nuclear Medicine Society guidelines (15).

CKD was defined per standard parameters utilizing GFR for staging. Stage 1 was defined as kidney function with normal or increased GFR (>90 ml/min/1.73 m^2), stage 2 as mild reduction in GFR (60-89 ml/min/1.73 m^2), stage 3 as moderate reduction in GFR (30-59 ml/min/1.73 m^2), stage 4 as severe reduction in GFR (15-29 ml/min/1.73 m^2) and stage 5 as kidney failure (GFR <15 ml/min/1.73 m^2) (16).

Statistical analysis

The data were analyzed using R studio (version 3.6.1; R studio, Boston, Massachusetts). Statistical analysis was performed using the unpaired Student t test and one way ANOVA for continuous variables with parametric distribution, Mann-Witney's U test for those with nonparametric distribution and the chi-square test for categorical variables. The odds ratio (OR) along with 95% CIs for statistical significance were calculated using Medcalc statistical software (MedCalc Software 2018). P-values <0.05 were considered statistically significant.

Results

A total of 47 patients were included in the study. The TAF group consisted of patients that had switched from TDF to TAF (n= 17) and the TDF group consisted of patients that received TDF continuously (n= 30). As this was a real-world study, a subgroup of patients from the TDF group had not switched to TAF although they had low GFR and/or hypophosphatemia (TDF-CKD group) per their physician's discretion (n= 14).

Baseline characteristics of the patients

Table 1 summarizes the demographic and laboratory characteristics of the patients at entry to the study. There was a predominance of male sex in both groups (94% in the TAF group and 63% in the TDF group). The follow-up period was significantly shorter in the TAF group (13.7 vs. 35.5 months, p<0.001). Furthermore, the presence of diabetes mellitus in this group was significantly more common as compared with the TDF group (35% vs. 10%, p=0.03).

All the baseline parameters for the assessment of renal function are presented in Table 2. In line with the study protocol, both serum creatinine and GFR values regardless of the method used for their calculation were significantly lower in the TAF group as compared with the TDF group. The indication for transition to TAF was low GFR (<60 ml/min/1.73m^2) in 14/17 patients (82%), low serum phosphorus levels (<2.5 mg/dl) in 8/17 patients (47%) and solely osteoporosis in only 1/17 patients (6%). 6/17 patients (35%) were diagnosed at baseline both with CKD and hypophosphatemia.

Table 1. — **Baseline patient characteristics**

	TAF group	TDF group	p value
N	17	30	
Male sex, n (%)	16 (94.1)	19 (63.3)	0.020
Age, years	62,6 (9,9)	60,3 (9,2)	0.436
Follow-up duration, months	13,7 (6,5)	35,5 (22,7)	< 0,001
Time since transplantation, months	93,1 (61,3)	105,6 (75)	0.561
Hypertension, n (%)	10 (58.8)	11 (36.7)	0.142
Diabetes Mellitus (type II), n (%)	6 (35.3)	3 (10)	0.034
Serum albumin, g/dL	4,3 (0,47)	4,3 (0,34)	0.582
Hemoglobin, mg/dL	14 (1,7)	14,4 (1,4)	0.422
Alanine aminotransferase, IU/L	24,8 (12)	24,7(13,3)	0.994
Asparate aminotransferase, IU/L	29,9 (22,3)	25,6 (18,9)	0.495
Platelet count, 10^9/L	190,1 (80,6)	191,8 (96,5)	0.951
Cyclosporine Current use, n (%) Concentration, ng/mL	 3 (17.6) 43 (35)	 12 (40) 58,9 (33,8)	 0.114 0.487
Tacrolimus Current use, n (%) Concentration, ng/mL	 5 (29.4) 3,6 (1,5)	 11 (36.7) 6 (2,3)	 0.614 0.047
Everolimus Current use, n (%) Concentration, ng/mL	 8 (47.1) 3,8 (1,7)	 8 (26.7) 3 (1,4)	 0.156 0.371
Mycophenolate Mofetil Current use, n (%)	 12 (70.6)	 22 (73.3)	 0.840

Values are presented as mean (standard deviation) unless otherwise indicated. Reference ranges: alanine aminotransferase: 10-34; aspartate aminotransferase: 10-31.

Table 2. — **Baseline assessment of renal function**

	TAF group	TDF group	TDF-CKD group	p value
N	17	16	14	
Serum creatinine, mg/dL	1,27 (0,2)	1,02 (0,16)	1,06 (0,2)	0.002
rGFR, ml/min/1.73m^2	57,9 (12,1)	78,3 (13,6)	59,4 (11,8)	< 0.001
eGFR (CKD-EPI), ml/min/1.73m^2	61,6 (14,6)	77,8 (10,7)	66,2 (12,5)	0.003
eGFR (MDRD-6), ml/min/1.73m^2	63,2(14,1)	79,1 (12,7)	67,2 (11,8)	0,003
Serum phosphorus, mg/dL	2,7 (0,7)	3,1 (0,4)	3,1 (0,6)	0.129
Blood urea nitrogen, mg/dL	19,9 (5,4)	16,8 (5,1)	18,6 (5)	0.249

Values are presented as mean (standard deviation). rGFR: radionuclide technique-based Glomerular Filtration Rate; eGFR: estimated Glomerular Filtration Rate; CKD-EPI: Chronic Kidney Disease Epidemiology; MDRD: Modification of Diet in Renal Disease. Stages of renal function (ml/min/1.73 m^2): 1 >90; 2=60-89; 3=30-59; 4=15-29; 5 <15.Reference ranges: serum creatinine: 0.66-1.1 for female and 0.84-1.25 for male; serum phosphorus: 2.5-4.5; blood urea nitrogen: 4.67-20.07.

Changes in renal function

At the end of follow-up there were no significant changes in any marker of renal function (sCr, GFR, serum phosphorus) between the TAF and the TDF group. Figure 1 shows the changes in rGFR and eGFR between these groups. In addition, there were no significant changes in renal function between the TAF group and the TDF-CKD group (Figure 2). However, the numerical change in rGFR was greater in the latter comparison (ΔrGFR 3 vs. -2.14 ml/min, p=0.26). The changes in renal function per year were 3.27 and 0.6 for the TAF and TDF group

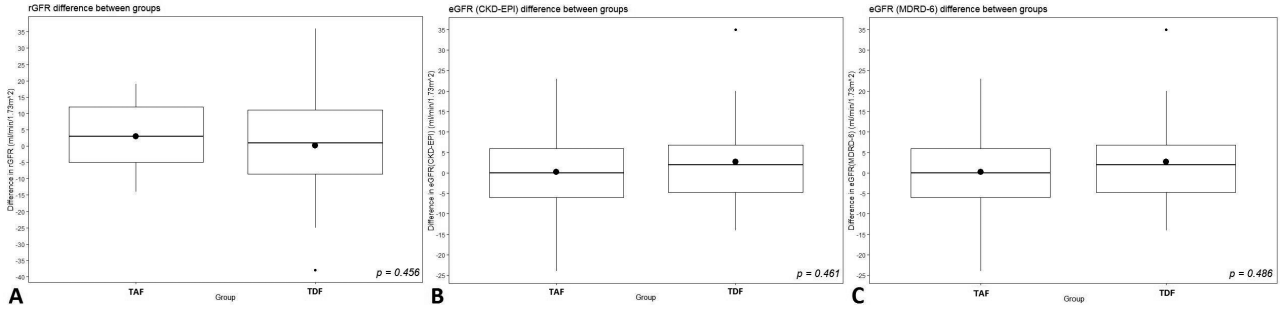

Figure 1. — Differences in rGFR and eGFR between the TAF and the TDF group.

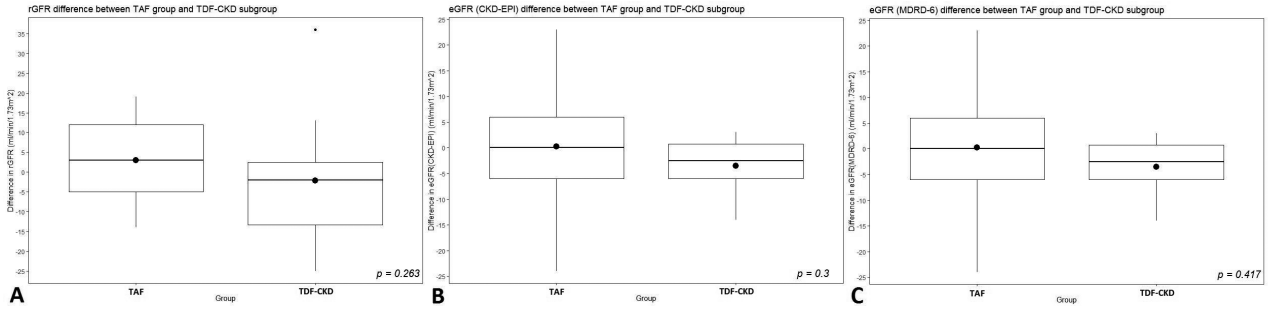

Figure 2. — Differences in rGFR and eGFR between the TAF and the TDF-CKD group.

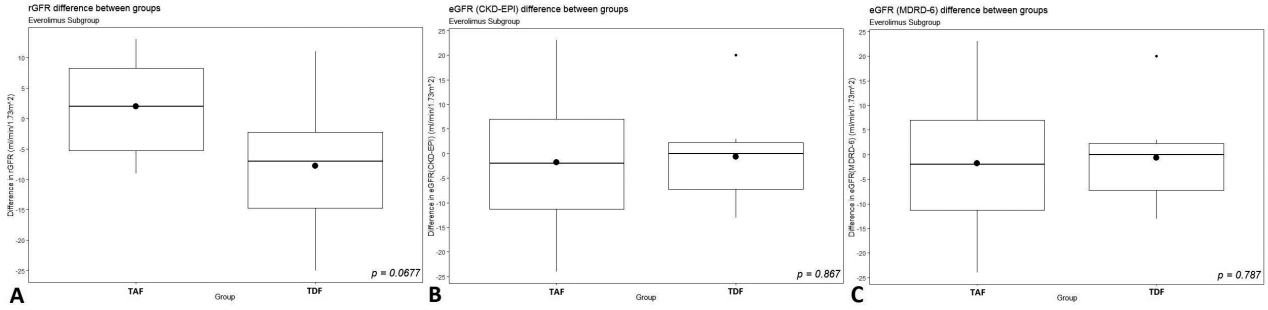

Figure 3. — Differences in rGFR and eGFR between the TAF and the TDF everolimus subgroup.

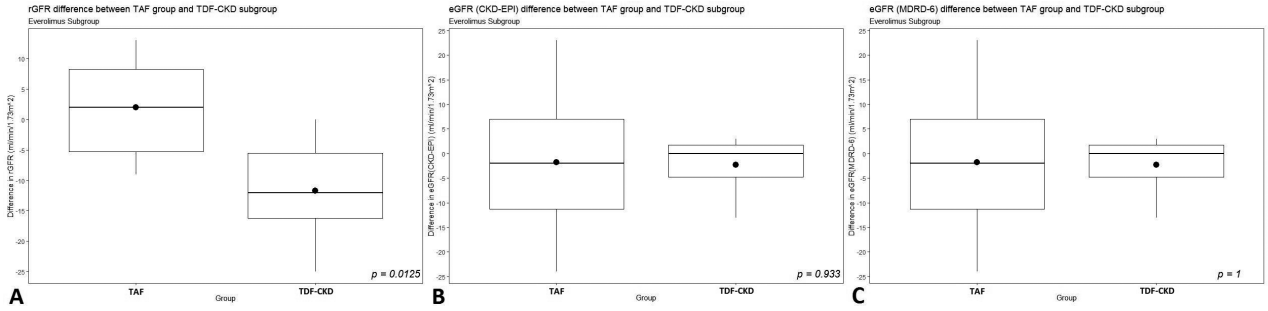

Figure 4. — Differences in rGFR and eGFR between the TAF and the TDF-CKD everolimus subgroup.

(p=0.298) and 3.6 and -0.676 for the TAF group and TDF-CKD group, respectively (p=0.306). rGFR returned to normal in 7/14 patients (50%) in the TAF group (OR 1.75, 95% CI 0.34-8.79); additionally serum phosphorus levels returned to normal in 3/8 patients (37.5%) in the same group (OR 0.6, 95% CI 0.05-6,79).

Prognostic factors

None of the established risk factors for kidney injury (age> 60 or 65 years, presence of arterial hypertension and/or diabetes mellitus, current CNI use) was associated with significant changes in renal function in the TAF group in univariate analysis and thus multivariate analysis was precluded. However, concurrent use of everolimus in the TAF group was associated with a significant improvement in rGFR values. Patients from the TAF group who received everolimus (n= 8) had a trend towards significant improvement in their renal function as compared with patients from the TDF group who also received everolimus (n= 8) (ΔrGFR 2 vs. -7.75

ml/min, p=0.06) (Figure 3). The changes in renal function per year in these groups were 1.95 and -4.24 (p=0.06). When the comparison was made between the TAF and the TDF-CKD group (n=6) the change in renal function was significant either as an absolute value (ΔrGFR 2 vs. -12 ml/min, p=0.01) (Figure 4) or as a change per year (1.95 and -6.52, p=0.02).

Safety issues

At the end of follow-up there were no significant changes between the TAF and the TDF group regarding the levels of transaminases or the concentration of immunosuppressants. TAF was well tolerated and no new or unexpected side effects were recorded during the study period. Finally, there were no cases of HBV recurrence or graft failure in neither group.

Discussion

Our study showed that switching from TDF to TAF for a period of almost 14 months cannot lead to a significant improvement of renal function in liver transplant recipients that have already developed CKD. Nonetheless, a numerically greater improvement was observed when the analysis was performed excluding those patients from the comparator group that received TDF and had not developed CKD. Patients that received everolimus as part of their immunosuppressive regimen had a significant improvement in their rGFR after switching from TDF to TAF implying that a combination of preventive measures should be implemented in order to preserve kidney function after LT. The changes in renal function in our study were not consistent across the different methods for assessing GFR emphasizing once more the need for precise evaluation of kidney function.

CKD is one of the leading non-hepatic causes of late morbidity and mortality in liver transplant recipients. The development of CKD is associated with an increased risk of death (approximately 4-fold) as compared to patients that do not develop this complication after LT(17). Despite the fact that TDF is associated with renal complications, most of the studies in the LT population have not shown a detrimental effect on renal function as compared to ETV (18). However, a more recent study has confirmed that TDF significantly increased the risk of proximal tubular dysfunction, although the effect of TDF on GFR was comparable to that of ETV (19). Taking into account the significance of CKD development and the documented nephrotoxic potential of TDF, it seems reasonable to avoid this drug in liver transplant recipients with CKD.

TAF, a prodrug of TDF, was developed to efficiently deliver the active metabolite to hepatocytes with less systemic exposure (20). Circulating concentrations of tenofovir have been found to be 90% lower after administration of TAF than after administration of TDF (21). This reduced systemic exposure offers the potential for an improved renal and bone safety profile, a benefit that has been already demonstrated in the registration trials of the drug (2,22,23). The results of these studies have shown less of a detrimental impact on renal function with TAF compared to TDF. In addition, switching from TDF to TAF was associated with an improvement in renal function in the non-transplant population with HBV infection (24).

The evaluation of GFR is superior to other renal markers, like serum creatinine, for the assessment of renal function. Estimating equations, including the MDRD and CKD-EPI formulae, are recommended for this purpose in the LT population (25). Although these formulae are the most widely used methods in routine clinical practice, the clearance of exogenous markers remains the gold standard for the assessment of GFR (26,27). In our center we perform rGFR measurements in predefined time intervals, typically every two years, or whenever this is clinically indicated. In the present study we used three different methods for the evaluation of GFR: i) the MDRD-6 variable; ii) the CKD-EPI sCr-based formula and iii) a radionuclide technique using either ^{51}Chromium-EDTA or ^{99m}Technetium-DTPA. It was recently shown that no clinically significant differences between the examinations performed with the two radioactive substances are present (28). Overall, rGFR methods are considered superior to estimating equations. Therefore we believe that the changes seen in rGFR in our study reflect in a more accurate way the changes in renal function than the changes in eGFR.

Data on the use of TAF in the LT population are very limited. In an open-label, phase 2 study in patients with CKD, switching to TAF was associated with a significant improvement in bone mineral density and a trend towards improvement in renal function as compared to continuous TDF treatment after 48 weeks (11). The median changes in rGFR in this study was 1.6 ml/min/1.73m^2 in the TAF group (n=26) vs. -1.1 ml/min/1.73m^2 in the TDF group (n=25). In a retrospective analysis, Sripongpun et al reported on 11 liver transplant recipients that were switched from TDF to TAF having stage 2 CKD at switch (mean baseline eGFR using the CKD-EPI formula was 63.9 ml/min/1.73m^2) (12). After 48 weeks, the median eGFR change was 2.5 mL/min/1.73 m^2, whereas in the 48-week period preceding the switch the corresponding change was 0.29 mL/min/1.73m^2. In another retrospective analysis on the impact of NA on renal function in patients after LT, TAF was found to have less of a harmful effect as compared to the rest of the antiviral agents (29). Essentially, GFR remained stable in patients receiving TAF after a mean period of less than a year (308 days). The authors also reported that only 6% (2/32) of patients receiving TAF had an increase in CKD stage by at least one stage as compared to 23% (11/47) of those never treated with TAF ($p < 0.05$).

Our results are in accordance with the previous studies in LT population showing that switching from TDF to TAF in patients that have already developed CKD

practically leads to a stabilization of renal function and not a robust improvement. We feel that this should not be necessarily interpreted as lack of effectiveness as liver transplant recipients may sometime enter a point of no return with regard to improving GFR. It seems possible that switching to TAF at an earlier point of time (the mean time after LT in our study was almost 8 years) or receiving TAF even from the peri-LT period may result in a more profound effect in preserving renal function. Studies with longer follow-up are also needed to clarify the magnitude and durability of this effect in regards to the longitudinal GFR changes. Another possible reason for the apparent lack of renal improvement is the multifactorial etiology of CKD in LT populations. Almost 60% of our study population suffered from concomitant arterial hypertension and approximately 1/3 of our patients were diabetic. Unfortunately, data on the management of these comorbidities (serial blood pressure and glucose measurements, glycated haemoglobin changes) were not available during the follow-up period of our study. In addition, CNIs were used during the study period in nearly 50% of our patients. In our center, CNI free regimens are often preferred in an attempt to preserve renal function. We have previously shown that early initiation of everolimus after LT can lead to significant improvement in GFR in patients with renal dysfunction post-LT (30,31). Subsequent randomized trials confirmed that early introduction of everolimus with gradual CNI withdrawal supported by mycophenolate mofetil co-administration is associated with a significant and durable renal benefit as compared to CNI-based immunosuppression (32,33). Whether therapy with TAF could have a synergistic effect with everolimus on renal function preservation is not currently clear, however both strategies seem to offer renal benefit and should be considered in the setting of CKD post-LT.

Our study has obvious strengths and limitations that have to be acknowledged prior to concluding. To our understanding this is the first real-world study with similar design in liver transplant recipients with CKD. Although the sample size was small to allow firm conclusions, it seems that it is hard to collect larger samples, unless multicenter studies are undertaken. Additional information that are lacking from our study would have improved the validity of our research. First, the availability of pre-LT data on renal function of our patients could have helped to study the impact of TAF in better characterized subgroups. Second, data on bone mineral density could have contributed to describe the overall beneficial effects of TAF in LT patients in a more comprehensive way.

In conclusion, TDF conversion to TAF in post-LT patients who have developed CKD and/or hypophosphatemia does not lead to improvement of kidney function after a period of approximately one year. It is likely that a combination of measures, including the use of TAF, will produce more profound improvements in renal function after longer follow-up periods post-LT. Liver transplant hepatologists should take into account this potential beneficial effect when choosing NA for HBV prophylaxis.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

Emmanouil Sinakos: Consultancy and research funding from Gilead Sciences

Ioannis Goulis: Consultancy and research funding from Gilead Sciences

Evangelos Akriviadis: Consultancy and research funding from Gilead Sciences

References

1. LAMPERTICO P, AGARWAL K, BERG T, BUTI M, JANSSEN HLA, PAPATHEODORIDIS G, *et al*. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017, **67**(2): 370-98.
2. AGARWAL K, BRUNETTO M, SETO WK, LIM Y-S, FUNG S, MARCELLIN P, *et al*. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. *J Hepatol*. 2018, **68**(4): 672-81.
3. BROUWER WP. Tenofovir alafenamide for hepatitis B: evolution or revolution? *lancet Gastroenterol Hepatol*. 2016, **1**(3): 174-5.
4. WONG GL-H, SETO W-K, WONG VW-S, YUEN M-F, CHAN HL-Y. Review article: long-term safety of oral anti-viral treatment for chronic hepatitis B. *Aliment Pharmacol Ther*. 2018, **47**(6): 730-7.
5. COOPER RD, WIEBE N, SMITH N, KEISER P, NAICKER S, TONELLI M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis*. 2010, **51**(5): 496-505.
6. KARA AV, YILDIRIM Y, OZCICEK F, ALDEMIR MN, ARSLAN Y, BAYAN K, *et al*. Effects of entecavir, tenofovir and telbivudine treatment on renal functions in chronic hepatitis B patients. *Acta Gastroenterol Belg*. 2019, **82**(2): 273-7.
7. WONG GL-H, TSE Y-K, WONG VW-S, YIP TC-F, TSOI KK-F, CHAN HL-Y. Long-term safety of oral nucleos(t)ide analogs for patients with chronic hepatitis B: A cohort study of 53,500 subjects. *Hepatology*. 2015, **62**(3): 684-93.
8. RODRIGUEZ-NOVOA S, ALVAREZ E, LABARGA P, SORIANO V. Renal toxicity associated with tenofovir use. *Expert Opin Drug Saf*. 2010, **9**(4): 545-59.
9. OJO AO, HELD PJ, PORT FK, WOLFE RA, LEICHTMAN AB, YOUNG EW, *et al*. Chronic Renal Failure after Transplantation of a Nonrenal Organ. *N Engl J Med*. 2003, **349**(10): 931-40.
10. PERUMPAIL R, KHEMICIAN S, LAKHOO K, DO A, CHOI G, DURAZO F, *et al*. PS-049-Tenofovir alafenamide for hepatitis B virus prophylaxis post-liver transplantation is associated with improved renal function: An interim analysis of a multicenter real-world experience. *J Hepatol*. 2019, **70**(1): e30-1.
11. GANE EJ GB, RAY-CHADHURI D *et al*. Safety and Efficacy at 1 Year in Post–Liver Transplant Patients With Chronic Kidney Disease Receiving Tenofovir Alafenamide for HBV Prophylaxis. *Hepatology*. 2018, **68**(S1): 1-183.
12. SRIPONGPUN P, MANNALITHARA A, KWO PY, KIM WR. Potential Benefits of Switching Liver Transplant Recipients to Tenofovir Alafenamide Prophylaxis. *Clin Gastroenterol Hepatol*. 2020, **18**(3): 747-9.
13. LEVEY AS. A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. *Ann Intern Med*. 1999, **130(6)**: 461.
14. LEVEY AS, STEVENS LA, SCHMID CH, ZHANG Y (Lucy), CASTRO AF, FELDMAN HI, *et al*. A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med*. 2009, **150**(9): 604.
15. FLEMING JS, NUNAN TO. The new BNMS guidelines for measurement of glomerular filtration rate. *Nucl Med Commun*. 2004, **(8)**: 755-7.

16. LEVEY AS, CORESH J. Chronic kidney disease. *Lancet*. 2012, **379**(9811): 165-80.
17. WATT KDS, PEDERSEN RA, KREMERS WK, HEIMBACH JK, CHARLTON MR. Evolution of Causes and Risk Factors for Mortality Post-Liver Transplant: Results of the NIDDK Long-Term Follow-Up Study. *Am J Transplant*. 2010, **10**(6): 1420-7.
18. CHOLONGITAS E, PAPATHEODORIDIS GV. High Genetic Barrier Nucleos(t)ide Analogue(s) for Prophylaxis From Hepatitis B Virus Recurrence After Liver Transplantation: A Systematic Review. *Am J Transplant*. 2013, **13**(2): 353-62.
19. LEE J, PARK JY, YANG SJ, LEE JY, KIM DG, JOO DJ, *et al*. Renal safety of tenofovir disoproxil fumarate and entecavir with hepatitis B immunoglobulin in liver transplant patients. *J Viral Hepat*. 2020, **27**(8): 818-25.
20. MURAKAMI E, WANG T, PARK Y, HAO J, LEPIST E-I, BABUSIS D, *et al*. Implications of Efficient Hepatic Delivery by Tenofovir Alafenamide (GS-7340) for Hepatitis B Virus Therapy. *Antimicrob Agents Chemother*. 2015, **59**(6): 3563-9.
21. AGARWAL K, FUNG SK, NGUYEN TT, CHENG W, SICARD E, RYDER SD, *et al*. Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. *J Hepatol*. 2015, **62**(3): 533-40.
22. CHAN HLY, FUNG S, SETO WK, CHUANG W-L, CHEN C-Y, KIM HJ, *et al*. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016, **1**(3): 185-95.
23. BUTI M, GANE E, SETO WK, CHAN HLY, CHUANG W-L, STEPANOVA T, *et al*. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016, **1**(3): 196-206.
24. KAY W, SETO WK, IZUMI N, LIM YS, KAO JH, STREINU-CERCEL A, *et al*. Bone and Renal Safety Are Improved in Chronic HBV Patients 1 Year after Switching to Tenofovir Alafenamide (TAF) from Tenofovir Disoproxil Fumarate (TDF). *Hepatology*. 2018, **68**(S1): 1-183.
25. LUCEY MR, TERRAULT N, OJO, HAY JE, NEUBERGER J, BLUMBERG E, *et al*. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transplant*. 2013, **19**(1): 3-26.
26. TRAYNOR J, MACTIER R, GEDDES CC, FOX JG. How to measure renal function in clinical practice. *BMJ*. 2006, **333**(7571): 733-7.
27. PIANO S, ROMANO A, DI PASCOLI M, ANGELI P. Why and how to measure renal function in patients with liver disease. *Liver Int*. 2017, **37**: 116-22.
28. MCMEEKIN H, BARNFIELD M, WICKHAM F, BURNISTON M. 99mTc DTPA vs. 51Cr EDTA for glomerular filtration rate measurement. *Nucl Med Commun*. 2019, **40**(12): 1224-9.
29. SAAB S, SONG D, CHALLITA YP, XIWEN ZHOU T, SAAB EG, VIRAMONTES MR, *et al*. Long-term outcomes with oral therapy in liver transplant recipients with hepatitis B. *Clin Transplant*. 2019, **33**(12).
30. CHOLONGITAS E, GOULIS I, THEOCHARIDOU E, ANTONIADIS N, FOUZAS I, IMVRIOS G, *et al*. Everolimus with or without mycophenolate mofetil in a liver transplantation setting: a single-center experience. *Ann Gastroenterol*. 2018, **31**(5): 613-20
31. CHOLONGITAS E, GOULIS I, THEOCHARIDOU E, ANTONIADIS N, FOUZAS I, GIAKOUSTIDIS D, *et al*. Everolimus-based immunosuppression in liver transplant recipients: a single-centre experience. *Hepatol Int*. 2014, **8**(1): 137-45.
32. SALIBA F, DUVOUX C, GUGENHEIM J, KAMAR N, DHARANCY S, SALAME E, *et al*. Efficacy and Safety of Everolimus and Mycophenolic Acid With Early Tacrolimus Withdrawal After Liver Transplantation: A Multicenter Randomized Trial. *Am J Transplant*. 2017, **17**(7): 1843-52.
33. SALIBA F, DUVOUX C, DHARANCY S, DUMORTIER J, CALMUS Y, GUGENEHEIM J, *et al*. Early Switch From Tacrolimus to Everolimus After Liver Transplantation: Outcomes at 2 Years. *Liver Transplant*. 2019, **25**(12): 1822-32.