Effects of entecavir, tenofovir and telbivudine treatment on renal functions in chronic hepatitis B patients

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Abstract

Background and study aims : **The aim of this study was to enlighten the controversy about the renal safety of entecavir, tenofovir, and telbivudine treatments in chronic hepatitis B (CHB) patients by comparing these treatments in real-world conditions.**

Patients and methods : **We retrospectively enrolled 104 treatment-naive patients with CHB monoinfection into our study. Patients were treated with entecavir monotherapy (n=38), tenofovir monotherapy (n=35), or telbivudine monotherapy (n=31). We then compared and statistically analyzed the effects of these drugs on the estimated glomerular filtration rate (eGFR) over a 24-month follow-up period.**

Results : **In the entecavir group, time-dependent change in eGFR was not statistically significant ($p = 0.357$). There was a statistically significant increase in eGFR in the telbivudine group at 12 months ($p < 0.001$) and at 24 months ($p < 0.001$) and, in contrast, a statistically significant decrease in the tenofovir group at 12 months ($p < 0.001$) and at 24 months ($p < 0.001$). There was no significant relationship between entecavir and eGFR change ($p = 0.763$). We found that tenofovir and telbivudine were independent predictors of eGFR change (decrease in eGFR, $p < 0.001$ and increase in eGFR, $p = 0.001$, respectively)**

Conclusions : **We recommend close follow-up of renal functions, especially for patients treated with tenofovir. Telbivudine was superior to the other drugs in terms of renal function. We conclude that an individualized therapy program considering treatment efficacy and side effects is the best option for patients.** (Acta gastroenterol. belg., **2019**, 82, **273-277**).

Key words : Chronic hepatitis B, estimated glomerular filtration rate, entecavir, tenofovir, telbivudine

Introduction

Hepatitis B is a viral infection that affects 257 million people worldwide and is a leading cause of liver cirrhosis and hepatocellular carcinoma. Thus, it is a global public health problem. In 2015, there were 887,000 deaths related to hepatitis B infection mostly from complications such as cirrhosis and hepatocellular carcinoma (1). The diagnosis of chronic hepatitis B (CHB) infection is based on the persistence of hepatitis B surface antigens (HBsAg) for more than six months. The goals of antiviral therapy are to suppress viral replication and to ensure the loss of related antigens. Currently, pegylated interferons and oral nucleoside/nucleotide analogs (NUCs) are the treatment options mostly used for CHB infection (2). The effectiveness of NUCs are evident, and their usage is easier as they are administered orally and have fewer side effects. But most patients require long-term treatment as premature discontinuation of NUC treatment may result in virological relapse and liver failure (3).

Long-term efficacy, safety, and costs are major determinants in choosing which NUC to use for first-line treatment (4). Lamivudine, telbivudine, and entecavir are approved as nucleoside analogs while tenofovir disoproxil fumarate (tenofovir) and adefovir dipivoxil are approved as nucleotide analogs for the treatment of CHB. But tenofovir, entecavir, and telbivudine are more widely used due to their superior virological, biochemical, and clinical efficacy. They also have a higher barrier to resistance and more tolerable side effect profiles (5-7). The kidney is the primary route for the excretion of NUCs so that nephrotoxicity can be encountered during usage of these agents. Although the exact mechanism of nephrotoxicity is not well known, it can be attributed to alterations in renal tubular transporters especially in the proximal renal tubules, as well as apoptosis and mitochondrial toxicity (8).

Although there are some data about tenofovir nephrotoxicity (9) and the renal protective effect of telbivudine (10), controversial results are also found in the literature about the renal effects of entecavir, tenofovir and telbivudine in the treatment of CHB patients (11,12). Our aim was to enlighten the controversy on this topic by comparing the renal safety of entecavir, tenofovir, and telbivudine in CHB patients.

Materials and methods

Out of 304 patients that were screened, 104 treatment-naive patients with CHB monoinfection were enrolled into this retrospective cohort study according to our inclusion and exclusion criteria (Figure 1). The patients were treated with entecavir monotherapy (n = 38), tenofovir monotherapy (n = 35), or telbivudine monotherapy (n = 31) between December 2012 and February 2015 at a public university hospital. Inclusion criteria for the study

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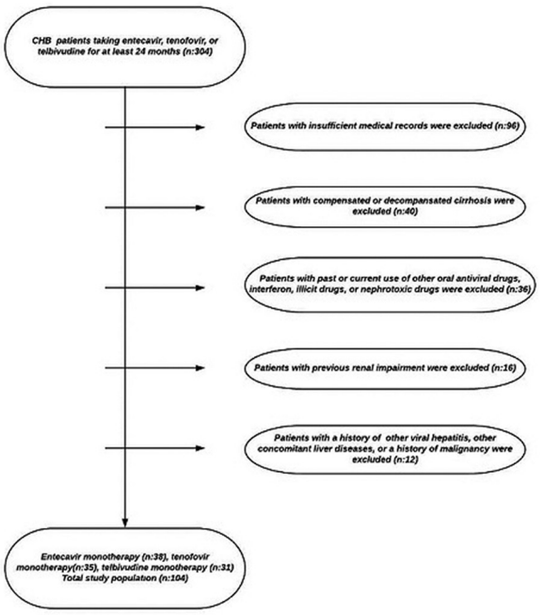

Figure 1. — Flowchart of the enrollment process.

were hepatitis B surface antigen (HBsAg) seropositivity, a pretreatment liver biopsy which was consistent with CHB and evaluated according to Ishak scoring system (13) , pretreatment serum hepatitis B virus (HBV) DNA levels, and positive or negative serology for hepatitis B envelope antigens (HBeAg). Patients with the following characteristics were excluded : age < 18 years old, previous use of oral antiviral treatments or interferon-alpha treatments, other viral infections such as hepatitis C, hepatitis D or human immunodeficiency virus (HIV), other concomitant liver diseases such as alcoholic liver disease or autoimmune liver disease, hepatocellular carcinoma or any other malignancy, cirrhosis, hepatic decompensation, solid organ transplantation, illicit drug use, nephrotoxic drug use, pregnancy, patients with a baseline estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m^2 as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (14), or patients missing baseline laboratory data. We excluded cirrhotic patients because we wanted to compare the effects of the drugs in as homogenous a patient group as possible. We also wanted to rule out the possible effects of cirrhosis on renal functions since some studies showed that even compensated cirrhosis can cause systemic hemodynamic changes and glomerular hyperfiltration (15, 16)

The following data were obtained from patient files : demographic data (age and sex), comorbidities (diabetes mellitus and hypertension), serum levels of HBV-DNA, degree of liver fibrosis, histology activity index, CHB serotype (positive or negative HBeAg), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and eGFR values. Renal function deterioration was defined as a decrease in eGFR from the initial baseline to the final visit. There is no clear definition of what a clinically significant decrease or increase in eGFR is ; therefore, a significantly different tendency in changes of eGFR levels during antiviral treatment was taken into consideration.

Statistical analysis

Results are presented for categorical variables as numbers and percentages, and for continuous variables as means ± standard deviations. Treatment and time effects on eGFR were evaluated by repeated measures ANOVA. The normality of the dependent variable in each combination of the related groups were confirmed by using the Shapiro-Wilk test of normality. Mauchly's Test of Sphericity was used to check the assumption of sphericity. If Mauchly's test statistic was significant, the Greenhouse-Geisser or Huynh-Feldt correction was used. If the main/interaction effect was significant, a Bonferroni correction was applied for multiple comparisons. According to our treatment groups, the values of eGFR over time are presented with a profile plot (Figure 2). Univariate and multivariate linear regression analyses were used to assess the factors predictive of

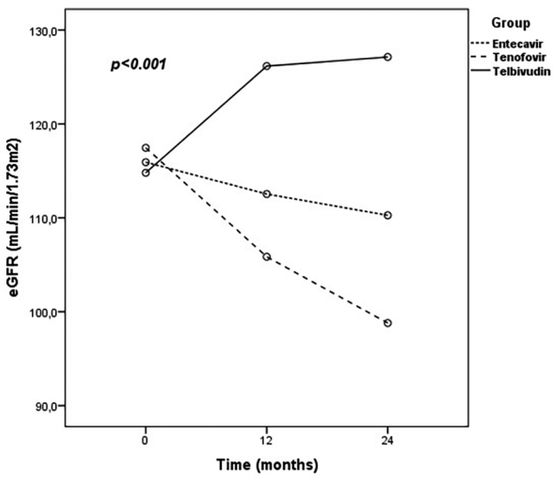

Figure 2. — Time-based changes in estimated glomerular filtration rate (eGFR) in the treatment groups and comparison between groups.

renal function deterioration. Thus, on the basis of the univariate analysis, any variable significantly related with predictive renal function deterioration, those with $p < 0.25$, were drawn into the analysis. Age and sex were included in the model as biological factors. The statistical level of significance for all tests was 0.05. Statistical analysis was performed using IBM SPSS version 19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY : IBM Corp.).

Results

Baseline characteristics of the 104 patients were examined and compared between the groups. There was no statistically significant difference between the

Table 1. — **Baseline characteristics of patients in the treatment groups**

	Entecavir	Tenofovir	Telbivudin	p*
	Mean±SD	Mean±SD	Mean±SD	
Age (years)	35,3±12,2	35,3±12,1	33,1±10,3	0.700
Male (%)	65	71	63	0.806
ALT (IU/L)	58.1±18.9	55.9±18.6	58.6±18.8	0.816
HBVDNA (log10 copies/ml)	5.7±1.3	5.4±0.9	5.3±0.9	0.279
HBeAg-positive (%)	32	27	33	0.804
Fibrosis score#	2,32±0,580	2,44±0,561	2,47±0,571	0.544
Histology activity index#	7,189±1,69	7,264±1,86	7,066±1,91	0.909
Serum creatinine (mg/dl)				
Baseline	0,73±0,1	0,72±0,1	0,73±0,1	0.940
12 months	0,75±0,1	0,84±0,1	0,61±0,1	<0.001
24 months	0,74±0,1	0,91±0,1	0,57±0,1	<0.001
eGFR (mL/min/1.73 m^2)				
Baseline	115,9±18,0	117,5±14,7	114,8±17,9	0.819
12 months	112,5±15,5	105,8±14,4	126,2±13,5	<0.001
24 months	113,1±15,9	98,8±17,2	127,1±14,3	<0.001

ALT: alanine aminotransferase, HBV: hepatitis B virus, HBeAg: hepatitis B envelope antigen, eGFR: estimated glomerular filtration rate. *: p value refers One way ANOVA between treatment groups. #:According to Ishak *et al.*(1995).

Table 2. — **Univariate and multivariate linear regression of predictive factors for time-based change in estimated glomerular filtration rate**

	Univariate			Multivariate		
Variable	β	SE	p	β	SE	p
Age (years)	-0,122	0,176	0,490	0,106	0,146	0,469
Sex (male)	-1,449	4,296	0,737	0,031	3,494	0,993
HBV DNA(log10 copies/ml)	-3,200	1,822	0,088	3,009	1,553	0,056
ALT (U/l)	0,035	0,110	0,753			
HbeAg (positive)	-2,104	4,399	0,633			
Fibrosis score	-0,707	3,588	0,844			
Histology activity index	-1,430	2,023	0,481			
Entecavir	1,274	2,674	0,763			
Tenofovir	-22,595	3,650	<0,001	-16,618	3,874	**<0,001**
Telbivudine	22,748	3,812	<0,001	13,704	4,052	**0,001**
Hypertension	1,536	7,520	0,839			
Diabetes mellitus	3,269	10,410	0,754			

ALT: alanine aminotransferase, HBV: hepatitis B virus, HBeAg: hepatitis B envelope antigen

groups according to age, sex, ALT and HBV-DNA levels, HBeAg positivity, fibrosis scores, histology activity index, baseline serum creatinine, or eGFR levels (Table 1). When we examined the comorbidities (diabetes mellitus and hypertension), there were four patients with diabetes mellitus (two in the telbivudine group, one in the tenofovir group and one in the entecavir group) and eight patients with hypertension (three in the telbivudine group, three in the tenofovir group and two in the entecavir group).

Time-based changes of eGFR in the treatment groups and comparison between groups are shown in Figure 2. In the entecavir group, time-dependent change is not statistically significant ($p = 0.357$). There was a statistically significant increase in eGFR in the telbivudine group at 12 months ($p < 0.001$) and at 24 months ($p < 0.001$) and, in contrast, a statistically significant decrease in the tenofovir group at 12 months ($p < 0.001$) and at 24 months ($p < 0.001$) in a time-dependent fashion.

We used linear regression analysis to define independent variables related with eGFR change.

There was no statistically significant relationship between entecavir and eGFR change ($p = 0.763$). But tenofovir and telbivudine were independently associated with eGFR change (decrease in eGFR, $p < 0.001$ and increase in eGFR, $p = 0.001$, respectively) (Table 2).

Discussion

NUCs have effectively been used in the treatment of CHB, but long-term treatment is required with these agents. Consequently, safety of these drugs is of great importance and requires close attention. Renal function is one of these safety concerns and needs to be closely monitored as the kidney is the main clearance route for these drugs. Alterations in renal tubular transporters, apoptosis, and mitochondrial toxicity may play role in NUC-associated nephrotoxicity. Proximal renal tubules are the main target (6). Sise et al. found that basic histological changes in tenofovir-associated renal toxicity included acute tubular necrosis (70%) and interstitial fibrosis (30%) (17).

Tenofovir associated nephrotoxicity has been shown in HIV-infected patients in a few studies (18,19). But in hepatitis B patients, there are controversial and limited data. Ha et al. found that tenofovir was not associated with significant deterioration of renal function (20). In a study of Korean CHB patients, researchers showed a low incidence of renal adverse events with tenofovir treatments (11). López et al. did not show any significant deterioration in renal function (21). A study of 50 CHB patients receiving tenofovir for more than 12 months found that the median eGFR level at the end of the follow-up period was lower than at the baseline by 6 mL/min/1.73 m^2 (22). Another 273 CHB patients received tenofovir for more than six months, and their eGFR levels at 24 months were lower than at their baseline (12). In a recently published cohort analysis, Jung et al. concluded that eGFR declined from the baseline in CHB patients given tenofovir treatment, and that the renal function of patients undergoing treatment with tenofovir should be monitored regularly (23). In our study, we also found a statistically significant decrease in eGFR in our tenofovir group from117.5 ± 14.7 mL/min/1.73 m^2at baseline to 105.8 ± 14.4 mL/min/1.73 m^2 after 12 months and to 98.8 ± 17.2 mL/min/1.73 m^2after 24 months, and we conclude that tenofovir is an independent risk factor for renal function deterioration.

There are also several studies about the effects of nucleoside analogs on renal function in the literature (24). Studies have generally shown that, with entecavir, renal function was not altered (25,26), although a few studies showed a slight reduction or increase in eGFR with entecavir treatment (27,28). Studies of telbivudine have shown that eGFR was either not modified or even increased (8,29). Yang et al. reviewed the literature and found that tenofovir and entecavir could, at least, be associated with reductions in renal function (30). At the end of a five-year study of a Spanish cohort of 611 CHB patients, there was a decrease in eGFR in the tenofovir group and an increase in eGFR in the entecavir group (31). In a study conducted with HBV-related compensated cirrhosis patients, and after two years of treatment, patients given telbivudine had a significantly higher eGFR compared to their baseline. However, patients given entecavir had a lower, although statistically not significant, eGFR compared to their baseline (32). In our study, we found no statistically significant change in eGFR in the entecavir group but a statistically significant increase in the telbivudine group at 12 months and 24 months (mean eGFR :114.8 ± 17.9 mL/min/1.73 m^2at baseline to126.2 ± 13.5 mL/min/1.73 m^2after 12 months and to127.1 ± 14.3 mL/min/1.73 m^2after 24 months). The effect of telbivudine on serum angiotensin-converting enzyme levels may be the reason for this improvement, as suggested by Liang et al., although we believe this to be an inadequate explanation (33).

Our study was conducted under real-world conditions with treatment-naive CHB patients. Effects of each of the three drugs on eGFR were retrospectively evaluated over a 24-month period and compared to each other. Our results are compatible with the general outcomes in the literature. There was no statistically significant difference between groups in terms of demographic, clinical, or laboratory parameters. Therefore, our results can make a significant contribution to the literature and to the related studies.

Limitations of our study were its retrospective nature and limited sample size. Due to the retrospective nature of the study, we did not know why one medication was chosen over the others for each patient. A selection bias may have been made when therapy was initiated. There is no clear consensus on what is clinically significant decrease or increase in eGFR when defining the deterioration or improvement, respectively, of kidney function. Therefore, we have only described a significant difference tendency in change of eGFR levels during antiviral treatments. Randomized controlled studies with larger sample sizes and long-term follow-ups should be made.

In conclusion, we suggest close follow-up of renal functions especially for those patients treated with tenofovir. Telbivudine was superior to the other drugs in terms of renal function. We recommend that individualized therapy, considering both treatment efficacy and side effects, is the best option for patients.

Conflict of Interest

There is no conflict of interest, and that all authors have read and approved of the manuscript being submitted.

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