Original Article

Adefovir, Tenofovir and Entecavir Renal Abnormality in Chronic Hepatitis B Patients

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Background: Renal dysfunction has been reported in chronic hepatitis B (CHB) patients treated with adefovir and tenofovir. However, few studies to date have measured estimated glomerular infiltration rate (eGFR) function in treatment of chronic hepatitis B with nucleos(t)ide analogs as well as reported eGFR function in long term treatment.

Objective: To evaluate the incidence and magnitude of decrease in eGFR in patients with long-term treatment of CHB with adefovir, tenofovir, and entecavir.

Materials and Methods: This is a retrospective cohort study of adult CHB patients who met treatment indication and treated with adefovir, tenofovir, or entecavir. Patients were excluded if there were co-infected with hepatitis C, hepatitis D, or HIV, decompensated cirrhosis at treatment initiation, baseline eGFR <50 ml/min. The patients were followed and compared cumulative incidence of renal dysfunction between the 3 study groups. Renal dysfunction was defined by decreased in eGFR ≥20% from baseline (MDRD 2 formula). Associated risk factors of renal dysfunction in long term treatment of CHB with oral nucleos(t)ide analogs were identified.

Results: Of all 528 patients (180, 128, and 220 patients in adefovir, tenofovir, and entecavir groups, respectively), we found a significant difference in the incidence and magnitude of decrease in eGFR in patients treated with adefovir compared with tenofovir and entecavir. The incidences of renal dysfunction in the adefovir, tenofovir, and entecavir groups at 1 year follow-up were 18.9%, 7.8%, and 7.3%, respectively (p = 0.001). After adjustment for age, sex, hypertension, diabetes, and cirrhosis, treatment with adefovir 10 mg/day was found to be a significant predictor for decreasing in eGFR of ≥20% (OR 2.85, p<0.001).

Conclusion: We observed greater incidences of renal dysfunction as measured by decrease in eGFR in patients treated with adefovir 10 mg/day when compared with tenofovir 300 mg/day and entecavir 0.5 mg/day.

Keywords: Chronic hepatitis B, Renal dysfunction, Oral nucleos(t)ide

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Chronic hepatitis B (CHB) remains the significant public health problem worldwide. According to the World Health Organization estimates, one third of the world population have been exposed to hepatitis B virus (HBV), about 350 million people have CHB infection and 600,000 die each year from HBV-related liver disease or hepatocellular carcinoma[1-3].

Currently, there are many drugs that approved for the treatment of CHB such as pegylated interferon-alpha, oral nucleoside or nucleotide analogues (NA). The goal of treatment is suppression of HBV viral replication, improvement in hepatic inflammatory disease and the reduction of long-term liver sequelae, including cirrhosis, decompensated cirrhosis and hepatocellular carcinoma[4,5].

NAs are oral agents that can be grouped by structure and function into 3 groups, L-nucleosides, acyclic phosphonates and others. All NAs are eliminated unchanged in the urine by a combination of glomerular filtration and proximal tubular secretion. Adefovir and tenofovir are among acyclic phosphonate group. The major adverse event of this class is tubular nephrotoxicity. Adefovir was found associated with proximal tubular dysfunction and Fanconi syndrome in HIV infection at dose of 60, 120 mg daily[6,7] and incidence of nephrotoxicity at 48 week was reported in 13%, 27% and 50% for adefovir doses of 30 mg, 60 mg, and 120 mg, respectively[8]. Although significant elevation in creatinine level was absent for a 10 mg dose at 48 weeks in CHB patients[9-11] but increased in serum creatinine level and proximal tubular dysfunction such as albuminuria, hypophosphatemia had been reported at 5 year of treatment[12,13].

Serum creatinine alone is not an accurate measurement of renal function. A given of serum creatinine level may present difference levels of creatinine clearance and renal function depending on patient body weight, age and race; therefore, such definition of renal impairment as used in clinical trials of adefovir may underestimate the

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incidence of clinically significant renal impairment. According to the National Kidney Foundation practice guideline for chronic kidney disease, serum creatinine concentration alone should not be used to access the level of kidney function[14]. Evaluating patient's estimated glomerular infiltration rate (eGFR) level using the Cockcroft-Gault formula [(140-age) x (weight in kilograms) x (0.85 if female)/(72 xCr)] or MDRD 2 formula [GFR = 186 x $[SCr]^{-1.154}$ x $[Age]^{-0.203}$ x [0.742 if patient is female] x [1.212 if patient is black]] yield the best indication of current kidney function[14], because it accounts for creatinine level, weight, age and sex.

To date, there was one retrospective study comparing treatment between adefovir 10 mg and entecavir 0.5 or 1 mg in CHB patient at 18 months to determine eGFR in 145 patients in each group. This study found 22% and 7% decrement of eGFR in adefovir and entecavir respectively[15]. Female, older age than 50 year, and baseline eGFR lower than 80 ml/min were predictors of significant decrease in eGFR[15].

For tenofovir, nephrotoxicity is classified as proximal tubular dysfunction with preserved renal function and proximal tubular dysfunction with decreased renal function in severe cases. Most cases of tenofovir associated nephrotoxicity were reported in HIV patients. Fanconi-like syndrome or nephrogenic diabetes insipidus can occurred in long term treatment[16-20]. Systematic reviews and meta-analysis had showed significant renal impairment after 1 year of treatment with tenofovir composing antiretroviral regimens[21]. One prospective study had been reported 0 to 1% hypophosphatemia in tenofovir treatment chronic hepatitis B patients at 72 week. No patient had creatinine clearance below 50 mL/min[20].

Few studies to date have measured eGFR function in the treatment of CHB with NAs as well as reported eGFR function in long-term treatment. Thus, the aim of this study was to evaluate the incidence and magnitude of decreased eGFR in patients with long-term treatment of CHB with adefovir, tenofovir, and entecavir.

Materials and Methods

Study design

This is a retrospective cohort study of CHB patients who met treatment indication. The patients were male or female, age over 18 years old who were treated with adefovir, tenofovir, or entecavir between July 1, 2003 and February 28, 2012. All patients were treated at Hepatitis Clinic, Siriraj Hospital, Bangkok, Thailand. The study groups consisted of patients who were prescribed 10 mg/day of adefovir monotherapy or in combination with 100 to 150 mg/day of lamivudine (group 1), 300 mg/day of tenofovir monotherapy or combination with 100 to 150 mg/day of lamivudine (group 2), and 0.5 mg/day of entecavir monotherapy (group 3). Patients were excluded if there were co-infected with hepatitis C, hepatitis D, or HIV, decompensated cirrhosis at treatment initiation, baseline eGFR <50 ml/min, prior treatment with other oral NAs (except lamivudine), and concomitant malignancy.

Data collection

All available medical records were retrieved including age, gender, alcoholic drinking, underlying disease (diabetes mellitus and hypertension), concurrent potential nephrotoxic drugs, body weight, height, evidence of cirrhosis, HBeAg, HBV DNA viral load, and serum creatinine, eGFR at baseline and during follow-up including concurrent potential nephrotoxic drugs serum creatinine, eGFR, spot serum phosphate, and urinalysis. eGFR was calculated using the MDRD 2 formula as above mentioned. Cirrhosis was defined by one or more of the followings; the presence of stage 4 fibrosis on histology, imaging evidence, presence of signs of portal hypertension (platelet count <100,000, splenomegaly, ascites, encephalopathy, or presence of varices).

Outcomes

We followed and compared the cumulative incidence renal dysfunction between the three study groups as primary outcome. Renal dysfunction was defined as decreased in eGFR ≥20% from baseline (MDRD 2 formula). Risk factors of renal dysfunction will be identified. Moreover, we performed spot urine examination to evaluate the prevalence of non-diabetic glycosuria, albuminuria, and hypophosphatemia.

Statistical analysis

Descriptive statistic was reported as number and percentage for categorical variables and mean ± standard deviation (SD) or median (range) for continuous variables. Comparison of qualitative data among 3 drug groups was performed using Pearson's Chi-square test. One-way ANOVA or Kruskal-Wallis test was used to compare quantitative variables among 3 drugs. The Kaplan-Meier method and log-rank test were used to assess the proportion of patients who maintain their renal function during treatment for CHB in each drug group. Independent variables with univariate *p*-value less than 0.2 or variables of interest were entered into binary logistic regression model to get the adjusted odds ratios and their 95% CIs. Statistical significance was defined with a two-tailed *p*-value <0.05. All statistical data analyses were performed using SPSS 18.0.

Results

Baseline characteristics

A total of 528 CHB patients were included in the data analysis, consist of 180 adefovir treated patients, 128 tenofovir treated patients, and 220 entecavir treated patients. The median duration of treatment (range) was 5 (1 to 6), 3 (1 to 5), and 4 (1 to 5) years for the adefovir, tenofovir, and entecavir groups, respectively.

Baseline characteristics for all groups are shown in Table 1. Sex, body mass index (BMI), and evidence of cirrhosis were similar among all 3 groups. Baseline serum creatinine and eGFR were comparable in all treatment groups. Mean age in the tenofovir group was lower than adefovir and entecavir groups (46.1±12.9 versus 51.4±9.5 and 53.4±10.4 [$p<0.001$ and $p<0.001$]). The tenofovir group had the highest

Table 1. Baseline characteristics of the patients

Baseline Characteristics	Adefovir (n = 180)	Tenofovir (n = 128)	Entecavir (n = 220)	*p*-value
Age, years (mean ± SD)	51.4±9.5	46.1±12.9	53.4±10.4	<0.001[+]
Male	125 (69.4)	88 (68.8)	143 (65.0)	0.599
BMI, kg/m^2	24.1±3.9	23.2±4.4	24.2±3.7	0.096
HBeAg-positive	24 (13.5)	68 (53.1)	64 (39.5)	<0.001
HBV DNA, $\log_{10}$ IU/mL	5.0±1.6	4.9±1.8	5.6±1.7	0.001[++]
Cirrhosis	55 (30.6)	43 (33.6)	70 (31.8)	0.853
Hypertension	37 (20.6)	18 (14.1)	65 (29.5)	0.003
Diabetes	25 (13.9)	10 (7.8)	47 (21.4)	0.003
Current nephrotoxic drug	12 (6.7)	3 (2.3)	28 (12.7)	0.002
Serum creatinine, mg/dL	0.86±0.17	0.88±0.18	0.87±0.20	0.712
eGFR (MDRD 2), mL/min	94.63±18.57	95.45±20.53	94.41±25.69	0.913
Treatment duration, years	5 (1 to 6)	3 (1 to 5)	4 (1 to 5)	<0.001

* Values are expressed as the mean ± standard deviation, median (range), or number of patients (%).
[+] Adefovir vs. Tenofovir (*p*-value <0.001), Adefovir vs. Entecavir (*p*-value = 0.168), Tenofovir vs. Entecavir (*p*-value <0.001).
[++] Adefovir vs. Tenofovir (*p*-value = 0.989), Adefovir vs. Entecavir (*p*-value = 0.004), Tenofovir vs. Entecavir (*p*-value = 0.003).

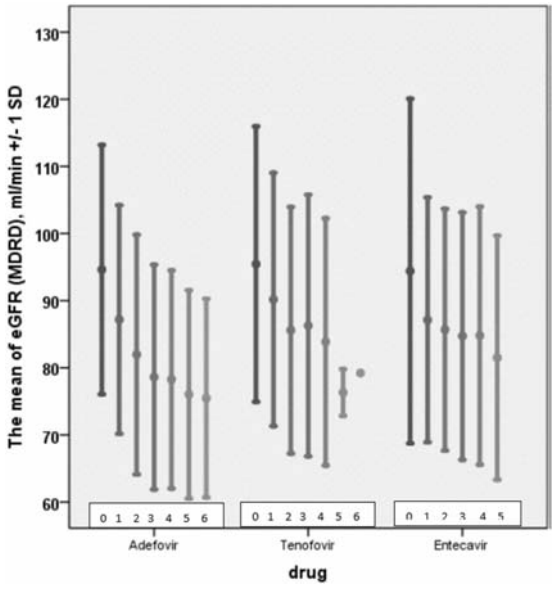

Figure 1. Mean of eGFR (MDRD) at year 0, 1, 2, 3, 4, 5, and 6.

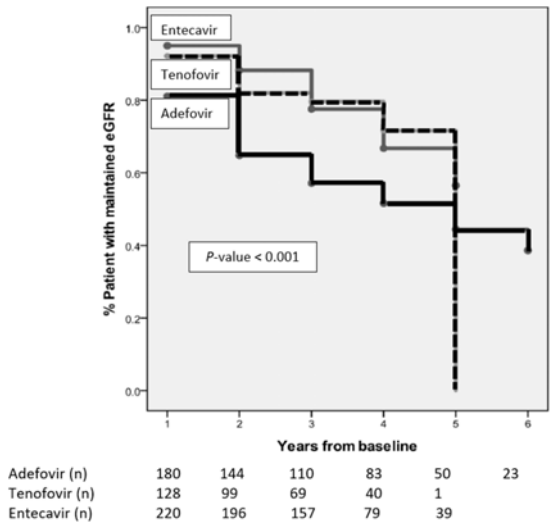

Figure 2. Percentage of patients who can maintain eGFR (mL/min) (<20% decrease from baseline).

proportion of HBeAg-positive (53.1%) as compare with entecavir group (39.5%) and the adefovir group (13.5%). Baseline HBV DNA level in the entecavir group was higher than the adefovir and tenofovir groups (5.6±1.7 versus 5.0±1.6 and 4.9±1.8 [p = 0.004 and p = 0.003]). Hypertension, diabetes mellitus, and concurrent potential nephrotoxic drugs in entecavir group were higher than the adefovir and tenofovir groups.

Changes of renal function during treatment

Of all 528 patients treated with adefovir, tenofovir, or entecavir, mean eGFR (MDRD 2) ±SD at baseline and follow-up period were shown in Figure 1. There was a statistically significant difference in number of incidences of renal dysfunction (incremental decrease in eGFR of ≥20%) in the adefovir group versus the tenofovir and entecavir groups (at 1-year follow-up, 18.9% vs. 7.8% and 7.3% [p = 0.001]). Figure 2 shows the proportion of patients who maintained their eGFR within 20% from baseline was also significantly lower in the adefovir group when compared with the tenofovir and entecavir groups using the Kaplan-Meier method (p<0.001).

Predictors for renal dysfunction

Table 2 describes univariate and multivariate

Table 2. Predictors for Decrease in eGFR ≥20% from baseline

Patient characteristic	Univariate analysis		Multivariate analysis	
	Crude odds ratio (95% CI)	*p*-value	Adjusted odds ratio (95% CI)	*p*-value
Age >50 years	1.12 (0.75 to 1.68)	0.583	1.16 (0.81 to 1.67)	0.410
Male	0.99 (0.66 to 1.48)	0.940	0.98 (0.67 to 1.43)	0.905
Hypertension	0.69 (0.41 to 1.17)	0.167	0.84 (0.54 to 1.30)	0.434
Diabetes	1.04 (0.60 to 1.81)	0.895	1.04 (0.63 to 1.70)	0.884
Cirrhosis	1.25 (0.83 to 1.89)	0.285	1.25 (0.85 to 1.82)	0.257
Concurrent nephrotoxic drug	1.52 (0.79 to 2.90)	0.207	1.34 (0.77 to 2.33)	0.304
Adefovir	2.93 (1.92 to 4.48)	<0.001	2.85 (1.88 to 4.32)	<0.001
Tenofovir	0.76 (0.44 to 1.29)	0.303	0.73 (0.44 to 1.22)	0.229

Table 3. Prevalence of non-diabetic Glucosuria, Albuminuria, and Hypophosphatemia

	Adefovir*	Tenofovir*	Entecavir*
Non-diabetic glucosuria [+] (n = 53/41/24)	3 (5.7)	1 (2.4)	0
Non-diabetic albuminuria [++] (n = 52/40/24)	8 (15.4)	3 (7.5)	0
Hypophosphatemia (n = 176/120/133)	6 (3.4)	1 (0.8)	0

* Values are expressed as the number of patients (%).
[+] Excluded patients who have diabetes or glucosuria at baseline.
[++] Excluded patients who have diabetes or albuminuria at baseline.

predictors and adjusted odd ratios for incremental decrease in eGFR of ≥20%. On multivariate analysis, independent predictor of ≥20% decrease in eGFR was only treatment with 10 mg/day of adefovir (adjusted OR 2.85, p<0.001).

Prevalence of tubular dysfunction

Table 3 shows prevalence of non-diabetic glucosuria, albuminuria, and hypophosphatemia. Three patients (5.7%) in the adefovir group and only one patient in the tenofovir group (2.4%) had non-diabetic glucosuria. Eleven patients had albuminuria, eight patients (15.4%) in the adefovir group and three patients (7.5%) in the tenofovir group. Six patients (3.4%) in the adefovir group and one patient (0.8%) in the tenofovir group experienced a persistent reduction in serum phosphate <2 mg/dl. Figure 3 shows the mean (95% CI) of serum phosphate at baseline and follow-up period. Serum phosphate in adefovir group had a trend to decline.

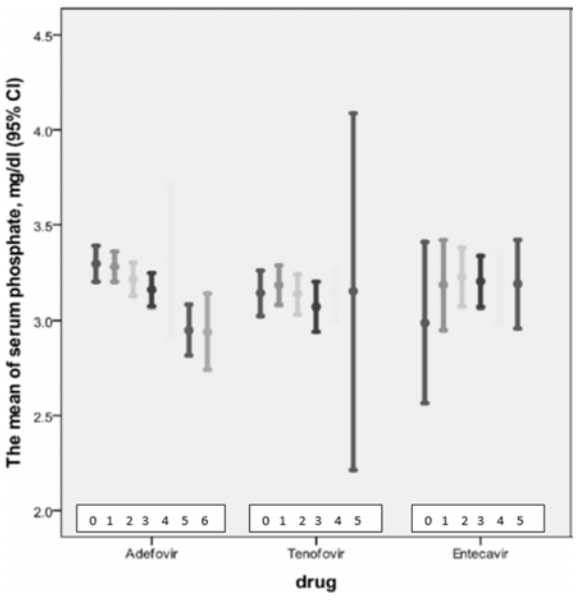

Figure 3. Mean of serum phosphate at year 0, 1, 2, 3, 4, 5, and 6.

Discussion

There are many alternative treatments for CHB, adefovir remains one of the more common therapies, because it was the first NA to recue lamivudine failure. The lower rate of resistance and slower onset of developing resistance in adefovir compared with lamivudine made it more ideal for long-term treatment of CHB in early 2000[22]. Although newer and improved agents are now available, patients currently treated with 10 mg of adefovir with sustained viral suppression are generally kept on their current treatment.

Previous studies have shown that adefovir nephrotoxicity is dose-related, and a great number of renal dysfunction incidences were reported[6-8,22]. Nevertheless, incidence of renal dysfunction may be under reported, because previous studies have reported renal dysfunction based primarily on serum creatinine level. We analyzed the data

using calculated eGFR for indication of renal dysfunction, because eGFR would better reflect renal function.

We found a significant difference in the incidence and magnitude of decrease in eGFR in patients treated with adefovir compared to tenofovir and entecavir. The incidence of renal dysfunction (incremental decrease in eGFR of ≥20%) in the adefovir, tenofovir, and entecavir groups at 1-year follow-up were 18.9%, 7.8%, and 7.3%, respectively. The proportion of patients who maintained their eGFR within 20% from baseline was also significantly lower in the adefovir group when compared with the tenofovir and entecavir groups in 5-, 3-, and 4-years of the median treatment duration of respective NA. After adjustments for age, sex, hypertension, diabetes, and cirrhosis it was found that adefovir 10 mg/day was a significant predictor for decreasing in eGFR of ≥20% (OR 2.85).

In the past, physicians tend to monitor renal function through serum creatinine level rather than eGFR. The current recommendation is to monitor serum creatinine every 3 months in all patients who are predisposed to renal insufficiency and on adefovir for more than 1 year[22]. Clinicians managing patients with CHB treated with 10 mg/day of adefovir need to monitor eGFR to observe potential renal dysfunction and dose adjustment or terminate treatment accordingly. However, current recommendation still underestimates the significant decline of renal function, since many patients have significant drop in eGFR while creatinine is still normal. The prevalence of urinary abnormality in adefovir treated group was higher but the number of patients screened were quite low and clinically significant still need more data as well as the tendency in decreasing serum phosphate overtime after treatment. Direct monitoring of renal tubular function such as ratio of tubular maximum reabsorption of phosphate (TmP) to GFR, bone density as well as many markers of renal injury may be helpful in early detection of tubular dysfunction but it is not practical and will add more cost to treatment of CHB patients.

This study had some limitation since it is retrospective and there were very few patients monitored urine parameters. Most of adefovir and tenofovir treated patients were those who had failed lamivudine and the practice of treatment at the time of study enrolment was adding adefovir or tenofovir to lamivudine which was different from current practice of switching to tenofovir. However, the strength of this study is comparing 2 potential nephrotoxic NAs with entecavir.

Conclusion

We observed a greater incidence of renal dysfunction as measured by eGFR in patients treated with adefovir 10 mg/day when compared with tenofovir 300 mg/day and entecavir 0.5 mg/day. Patients treated with adefovir should be monitored more closely for signs of renal dysfunction with eGFR measurements rather than serum creatinine levels. Role of urinary testing for glycosuria, proteinuria and serum phosphate monitoring may be helpful but need more data. Over the period of study, both tenofovir and entecavir were safe.

What is already known on this topic?

Acyclic phosphonate NAs such as adefovir and tenofovir have potential nephrotoxicity but there were very few long-term study on eGFR of these NAs, especially compared with NA without potential nephrotoxicity.

What this study adds?

Long-tern use of NAs associated with eGFR dropped and adefovir has more significant dropped pf eGFR as compared with tenofovir and entecavir. It is important to monitor eGFR regularly, preferable every 3 months if adefovir is prescribed in order to discontinue or change NA is eGFR drops more than 20%.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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