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Telbivudine and adefovir dipivoxil combination therapy improves renal function in patients with chronic hepatitis B

A STROBE-compliant article

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Abstract

Few studies have addressed the impact of adefovir dipivoxil (ADV)-based combination therapy on the renal function of patients with chronic hepatitis B (CHB). This study evaluated the effects of ADV combined with other antiviral nucleotide analogs (NAs) on renal function of patients with CHB, and analyzed the risk factors for more than 20% reduction of baseline estimated glomerular filtration rate (eGFR).

The data of 164 patients with CHB were retrospectively analyzed in this study. Of the 164 patients, 42 received entecavir (ETV) combined with ADV (ETV + ADV group), 68 lamivudine (LAM) combined with ADV (LAM + ADV group), and 54 telbivudine (LDT) combined with ADV (LDT + ADV group). Serum creatinine (SCr) level, eGFR, and proportion of patients with eGFR ≥ 90 mL/min/1.73 m^2 were observed. Also, the independent risk factors for more than 20% reduction of baseline eGFR were analyzed.

After 104-week combination therapy, compared with the baseline level, SCr levels were significantly increased in the ETV + ADV group (67 μmol/L vs 73 μmol/L, $P = .012$) and LAM + ADV group (68 μmol/L vs 79 μmol/L, $P = .008$), but it was significantly decreased in the LDT + ADV group (69 μmol/L vs 64 μmol/L, $P = .023$). Compared with the baseline level, eGFR was significantly decreased in the ETV + ADV group (107.8 mL/min/1.73 m^2 vs 96.1 mL/min 1.73/m^2, $P = .004$), and LAM + ADV group (105.4 mL/min/1.73 m^2 vs 87.3 mL/min/1.73 m^2, $P = .000$), but it was significantly increased in the LDT + ADV group (104.1 mL/min 1.73/m^2 vs 116.2 mL/min/1.73 m^2, $P = .005$). The proportion of patients with normal renal function (≥90 mL/min/1.73 m^2) was significantly higher in the LDT + ADV group than in the ETV + ADV group ($P = .002$) and LAM + ADV group ($P = .001$). Multivariate analysis showed that age ($P = .035$), male ($P = .005$), baseline eGFR ($P < .001$), LAM combined with ADV ($P < .008$), and ETV combined with ADV ($P = .03$) were independent risk factors for 20% reduction of baseline eGFR.

As compared with ETV and ADV combination therapy as well as LAM and ADV combination therapy, LDT and ADV combination therapy can improve eGFR level, so LDT and ADV combination therapy is suitable for the patients with potential renal impairment.

Abbreviations: ADV = adefovir dipivoxil, CHB = chronic hepatitis B, eGFR = estimated glomerular filtration rate, ETV = entecavir, LAM = lamivudine, LDT = telbivudine, NA = nucleotide analog, SCr = serum creatinine.

Keywords: adefovir dipivoxil, chronic hepatitis B, glomerular filtration rate, telbivudine

1. Introduction

The purpose of treatment for chronic hepatitis B (CHB) is to repress the replication of hepatitis B virus (HBV) and prevent liver disease progression.[1] Patients with CHB require long-term oral nucleotide analogs (NAs) to obtain remission and/or serologic response.[2] However, the 5-year resistance rates of lamivudine (LAM) and adefovir dipivoxil (ADV) are 66%[3] and 29%,[4] respectively. For telbivudine (LDT), 4-year resistance rate is 10%.[5] In patients with CHB, liver failure and hepatocellular carcinoma readily occur after virologic breakthrough.[6] Increasing evidence shows that ADV-based combined antiviral therapy has become a good option for treatment of CHB.[7] In recent year, more and more patients have received such combined treatment.[2] These oral antiviral NAs are metabolized and excreted by kidneys.[8] The long-term NA combination therapy exhibits good therapeutic effects and at the same time, useful clinical experience has been accumulated, but there still are some problems. Previous studies have shown that ADV alone can decrease estimated glomerular filtration rate (eGFR), but LDT alone can increase eGFR in the patients with CHB.[4,5,8] However, few studies have addressed the impact of ADV-based combination therapy on the renal function of patients with CHB who received ADV-based combination therapy after HBV resistance or no serologic response. This study evaluated the effects of ADV combined with other antiviral NAs on renal function of patients with CHB, and analyzed the risk factors for more than 20% reduction of baseline eGFR.

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Table 1

General data in the three groups (%, M [IQR]).

	ETV + ADV (n = 42)	LAM + ADV (n = 68)	LDT + ADV (n = 54)	*P*
Sex (male)	30 (71.4)	50 (73.5)	37 (68.5)	.831
Age, y	48 (21–58)	50 (25–65)	52 (20–60)	.123
ALT, U/L	86 (40–520)	102 (48–670)	93 (45–730)	.405
HBV DNA, lgcopies/mL	4.8 (3.2–8.7)	4.5 (3.1–8.3)	5.1 (3.0–8.9)	.253
SCr, μmol/L	67 (43–86)	68 (35–103)	69 (39–94)	.813
eGFR, mL/min/1.73 m^2	107.8 (66.8–137.3)	105.4 (64.3–148.2)	104.1 (70.5–145.7)	.632
eGFR ≥ 90 mL/min/1.73 m^2	31 (73.8)	54 (79.4)	41 (75.9)	.781
eGFR: 60–90 mL/min/1.73 m^2	11 (26.2)	14 (20.6)	13 (24.1)	.781
Positive HBeAg	22 (52.4)	39 (57.3)	36 (66.7)	.341

ADV = adefovir dipivoxil, ALT = alanine transaminase, eGFR = estimated glomerular filtration rate, ETV = entecavir, HBeAg = hepatitis B e antigen, HBV = hepatitis B virus, LAM = lamivudine, LDT = telbivudine, M (IQR) = median (interquartile-range), SCr = serum creatinine.

2. Materials and methods

All study methods were approved by the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University. All the subjects enrolled into the study gave written informed consents to participate.

2.1. Subjects

From February 2007 to October 2015, a total of 223 patients with CHB were diagnosed and treated in liver clinic of our hospital. The inclusion criteria were consistent with diagnostic criteria from the *Guidelines of Prevention and Treatment for Chronic Hepatitis B*[9]; baseline eGFR > 60 mL/min/1.73 m^2; baseline serum creatinine (SCr) < 130 μmol/L; and follow-up time of more than 104 weeks. The exclusion criteria were a history of ADV usage; abnormal urine routine results; having edema, pleural effusion, celiac effusion, or severe cardiac insufficiency; and having tumor, hypertension, liver cirrhosis, diabetes, or kidney disease. Finally, 164 patients consistent with inclusion and exclusion criteria were enrolled in this study. The data of 164 patients with CHB were retrospectively analyzed. Of the 164 patients, 117 were man and 47 women with a mean age of 34 ± 6 years.

2.2. Treatment protocols

Combination therapy of ADV (10 mg/d) and LAM (100 mg/d) was given to the 68 patients that had showed resistance or poor serologic response during LAM monotherapy. Combination therapy of ADV (10 mg/d) and LDT (600 mg/d) was given to the 54 patients that had showed resistance or poor serologic response during LDT monotherapy. In addition, combination therapy of ADV (10 mg/d) and entecavir (ETV; 0.5 mg/d) was given to the 42 patients that had showed resistance or poor serologic response during LAM and ETV sequential monotherapies.

2.3. Detection

The SCr was determined using MODULP800 automatic biochemistry analyzer (Roche, Manheim, Germany) 52 and 104 weeks after combination therapy, respectively. And then eGFR was calculated according to the formula of modified diet in renal disease: $eGFR = 186 \times SCr^{-1.154} \times age\ (year)^{-0.203} \times (female \times 0.742) \times (black\ people\ 1.212)$.[10] eGFR was graded as normal: eGFR ≥ 90 mL/min/1.73 m^2; mild renal impairment: 60 ≤ eGFR < 90 mL/min/1.73 m^2; and moderate renal impairment 30 ≤ eGFR < 60 mL/min/1.73 m^2.[11]

2.4. Statistical analysis

Statistical treatment was performed using SPSS 20.0 software. Measurement data were expressed as median (interquartile range). Wilcoxon rank sum test was used to compare the data between pre- and posttreatment within each group. Kruskal–Wallish rank sum test was used in the comparison among multiple groups. In univariate and multivariate analyses, logistic formula was used to calculate odds ratio of each factor for eGFR. Chi-squared test or continuity correction test was used in the analysis of enumeration data. Statistical significance was established at $P < .05$.

3. Results

3.1. General data in the 3 groups

There were no statistical differences in age, sex, HBV DNA, alanine transaminase (ALT), SCr, eGFR, and HBeAg positive rate among the 3 groups (all $P > .05$, Table 1).

3.2. SCr in the 3 groups 52 and 104 weeks after combination therapy

After 52- and 104-week combination therapy, compared with the baseline level, SCr levels were significantly increased in the ETV + ADV group (67 μmol/L vs 69 μmol/L, $P = .053$; and 67 μmol/L vs 73 μmol/L, $P = .012$) and LAM + ADV group (68 μmol/L vs 72 μmol/L, $P = .041$; and 68 μmol/L vs 79 μmol/L, $P = .008$, but it was significantly decreased in the LDT + ADV group (69 μmol/L vs 67 μmol/L, $P = .062$; and 69 μmol/L vs 64 μmol/L, $P = .023$) (Fig. 1).

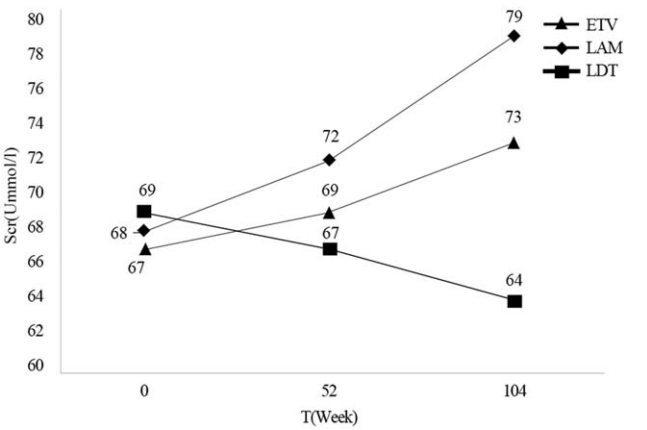

Figure 1. SCr levels in the 3 groups 52 and 104 weeks after combination therapy. ETV = entecavir, LAM = lamivudine, LDT = telbivudine, SCr = serum creatinine, T = time.

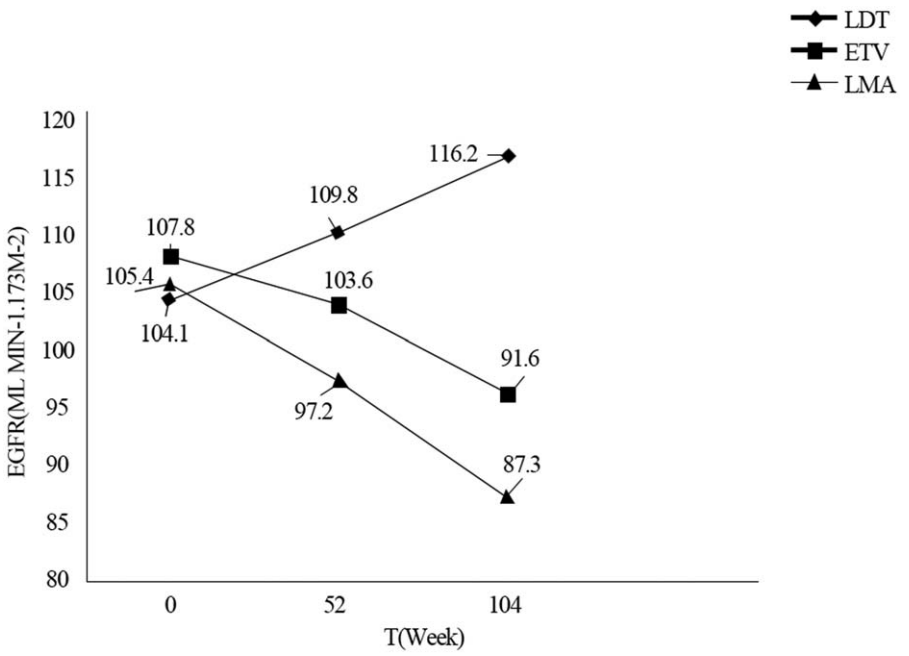

Figure 2. eGFR levels in the 3 groups 52 and 104 weeks after combination therapy. eGFR = estimated glomerular filtration rate, ETV = entecavir, LAM = lamivudine, LDT = telbivudine, T = time.

3.3. eGFR in the 3 groups 52 and 104 weeks after combination therapy

After 52- and 104-week combination therapy, compared with the baseline level, eGFR was significantly decreased in the ETV + ADV group (107.8 mL/min/1.73 m^2 vs 103.6 mL/min/1.73 m^2, $P = .028$; and 107.8 mL/min/1.73 m^2 vs 96.1 mL/min/1.73 m^2, $P = .004$) and LAM + ADV group (105.4 mL/min/1.73 m^2 vs 97.2 mL/min/1.73 m^2, $P = .024$; and 105.4 mL/min/1.73 m^2 vs 87.3 mL/min/1.73 m^2, $P = .000$), but it was significantly increased in the LDT + ADV group (104.1 mL/min/1.73 m^2 vs 109.8 mL/min/1.73 m^2, $P = .031$; and 104.1 mL/min/1.73 m^2 vs 116.2 mL/min/1.73 m^2, $P = .005$) (Fig. 2).

3.4. Injury degree of eGFR in the 3 groups 104 weeks after combination therapy

The proportion of patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2) was significantly higher in the LDT + ADV group than in the ETV + ADV group ($P = .002$) and LAM + ADV group ($P = .001$) 104 weeks after combination therapy. However, there was no statistical difference in the proportion of patients with normal renal function between the LAM + ADV group and ETV + ADV group ($P = .988$) (Table 2).

Compared with baseline level, eGFR increased by 20% or more in 15 patients 104 weeks after combination therapy. Of the 15 patients, 2 were from the ETV + ADV group, 1 from the LAM + ADV group, and 12 from the LDT + ADV group. Compared with baseline level, eGFR decreased by 20% or more in 37 patients 104 weeks after combination therapy. Of the 37 patients, 11 were from the ETV + ADV group, 25 from the LAM + ADV group, and 1 from the LDT + ADV group.

3.5. Analysis of independent risk factors for more than 20% reduction of baseline eGFR

Univariate analysis showed that age ($P = .003$), male ($P = .007$), baseline eGFR ($P < .001$), LAM combined with ADV ($P = .002$),

Table 2

Injury degree of eGFR in the 3 groups 104 weeks after combination therapy (mL/min/1.73 m^2), n (%).

Groups	Baseline level		104 wks later	
	eGFR, mL/min/1.73 m^2	n (%)	eGFR, mL/min/1.73 m^2	
			<90	≥90
ETV + ADV	<90	11 (26.20)	7 (63.63%)	4 (36.36%)
	≥90	31 (73.80)	9 (29.03%)	22 (70.97%)
Total		42	16 (38.10%)	26 (61.90%)
LDT + ADV	<90	13 (24.08)	4 (30.77%)	9 (69.23%)
	≥90	41 (75.92)	2 (4.88%)	39 (95.12%)
Total		54	6 (11.11%)*	48 (88.89%)*
LAM + ADV	<90	14 (20.58)	12 (85.71%)	2 (14.29%)
	≥90	54 (79.42)	14 (25.93%)	40 (74.07%)
Total		68	26 (38.24%)	42 (61.76%)

* $P < .05$ as compared with other 2 groups.

ADV = adefovir dipivoxil, eGFR = estimated glomerular filtration rate, ETV = entecavir, LAM = lamivudine, LDT = telbivudine.

Table 3

Analysis of independent risk factors for more than 20% reduction of baseline eGFR 104 weeks after combination therapy.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.07 (1.03–1.08)	.003	1.05 (1.01–1.07)	.035
Male	0.37 (0.22–0.72)	.007	0.24 (0.07–0.70)	.005
Baseline eGFR	0.92 (0.90–0.93)	<.001	0.90 (0.86–0.93)	<.001
ALT	0.98 (0.97–1.05)	.65	0.97 (0.92–1.03)	.57
HBV DNA	1.17 (0.98–1.40)	.057	0.87 (0.58–1.35)	.67
LAM/ADV	6.20 (3.23–11.85)	.002	6.67 (3.75–12.30)	.008
LDT/ADV	0.26 (0.10–0.61)	.005	0.96 (0.18–1.01)	.82
ETV/ADV	1.27 (0.47–2.13)	.56	1.08 (1.02–1.15)	.03

ADV = adefovir dipivoxil, ALT = alanine transaminase, CI = confidence interval, eGFR = estimated glomerular filtration rate, ETV = entecavir, HBV = hepatitis B virus, LAM = lamivudine, LDT = telbivudine, OR = odd ratio.

and LDT combined with ADV ($P = .005$) were correlated with 20% or more reduction of baseline eGFR. Multivariate analysis showed that age ($P = .035$), male ($P = .005$), baseline eGFR ($P < .001$), LAM combined with ADV ($P < .008$), and ETV combined with ADV ($P = .03$) were independent risk factors for more than 20% reduction of baseline eGFR (Table 3).

4. Discussion

The NAs can reduce HBV replication through inhibiting its DNA polymerase activity, but cannot eradicate HBV, thus long-term NA treatment has become a recognized effective anti-HBV strategy. Although previous studies have reported that NAs monotherapy affects renal function, ADV and tenofovir could potentially cause renal injury,[12,13] LAM and ETV treatment do not produced obvious renal toxicity, while LDT then shows protective effects on kidney.[13] It is necessary to determine that the changes of renal function in patients with CHB treated with ADV combined with LDT. The serum SCr level is associated with muscle metabolism, dietary intake, renal tubular secretion, and renal clearance, so serum Scr level varies greatly, which limits its application in evaluating mild impairment of renal function.[14,15] Therefore, we used eGFR to evaluate renal function in comparison of the effects of 3 different NA combination therapies on renal function of patients with CHB in this study.

Lee et al[16] observed 831 patients with CHB who received different NAs for 96 weeks, and found that eGFR levels were significantly increased in ADV + LDT group and ADV + LAM group, but it was significantly decreased in ADV + ETV group as compared with baseline level. Our results showed that the changes of Scr and eGFR were smaller in 52-week therapy than in 104-week therapy, suggesting that longer ADV and LDT combination therapy can produce better renal function improvement. LAM and ADV, as well as ETV and ADV combination therapies could increase Scr and decrease eGFR levels, while LDT and ADV combination therapy could decrease Scr and increase eGFR levels as compared to the baseline levels, which are similar to previous research results.[17]

Qi et al[17] found that eGFR level was increased by 12.52 mL/min/1.73 m^2 in the patients with mild baseline renal impairment and by 1.39 mL/min/1.73 m^2 in the patients with normal baseline renal function after LDT and ADV combination therapy; while after LAM and ADV combination therapy, eGFR level was decreased by 10.81 mL/min/1.73 m^2 in the patients with mild baseline renal impairment and by 20.46 mL/min/1.73 m^2 in the patients with normal baseline renal function. In these results,[16,17,18] the change over 20% baseline eGFR was regarded as obvious change of renal function. This study indicated that the numbers of patients with more than 20% reduction of baseline eGFR were significantly higher in the ETV + ADV (11 cases, 26.19%) and LAM + ADV (25 cases, 43.10%) groups than in the LDT + ADV group (1 case, 1.86%) 104 weeks after combination therapy; in contrast, the number of patients with more than 20% elevation of eGFR level was significantly higher in LDT + ADV group than in other 2 groups. These results suggest that the combination therapy of LDT and ADV can improve renal function, and can also allow the eGFR under the baseline to become normal. The combination therapy of ETV and ADV or LAM and ADV induced a reduction of eGFR level. For patients with CHB requiring long-term combination therapy, the security for eGFR has important clinical significance. Renal function is an important safety issue because in the patients with advanced liver disease, especially in the patients with decompensated liver cirrhosis caused by hepatitis B, renal insufficiency is associated with high mortality. This study indicated that baseline eGFR level was a factor for more than 20% reduction of eGFR. Among 13 patients with mild eGFR impairment of LDT + ADV group, the eGFR in 9 patients returned to normal after ADV and LDT combination therapy, showing that ADV and LDT combination therapy was suitable for the patients with mild eGFR impairment. Considering that most patients showing over 20% reduction of eGFR level were from the patients treated by ETV and ADV or LAM and ADV combination therapy, and multivariate analysis showed that age, male, baseline eGFR, LAM combined with ADV, and ETV combined with ADV were independent risk factors for more than 20% reduction of baseline eGFR, so ETV and ADV or LAM and ADV combination therapy was not recommended for the elderly patients, male patients and the patients with renal impairment.

Previous studies showed the ADV decreases eGFR through inhibiting the replication and synthesis of mitochondrial DNA (mtDNA).[19,20] However, LDT and ADV combination therapy could elevate eGFR level, indicating the protective role of LDT on the kidney which might help to counteract the renal toxicity of ADV. The mechanism that LDT improves renal function has been unclear. The LDT excretion in the kidney may be mediated by passive diffusion that cannot cause mtDNA depletion or toxic effects on renal tubular epithelial cell function.[21] LDT improves tubular dysfunction probably by increasing glomerular blood flow.[22] LDT-based combination therapy has protective effects on kidneys, so for the patients with potential renal impairment, LDT-based combination therapy may be used as rescue therapy.

This is a retrospective small-sample study with relatively short follow-up, and also the changes of urine protein, urine glucose,

blood pressure, serum phosphorus, and calcium were not determined during treatment. The influence of NA combination treatment on the renal function of patients with CHB remains to be further confirmed by the studies with larger sample and longer follow-up.

Author contributions

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