

Prospective Study

Early kidney injury during long-term adefovir dipivoxil therapy for chronic hepatitis B

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binding protein (RBP) excretion, and renal impairment with adefovir dipivoxil (ADV) for chronic hepatitis B.

METHODS: We enrolled 165 patients with chronic hepatitis B infection who were treated with ADV monotherapy ($n = 90$) or ADV plus lamivudine combination therapy ($n = 75$). An additional 165 chronic hepatitis B patients treated with entecavir were recruited as controls. We detected serum creatinine, urine β 2-M, and RBP levels, and estimated the glomerular filtration rate (eGFR) at the initiation of antiviral therapy and every 6 mo for a period of five years.

RESULTS: Urine β 2-M abnormalities were observed in patients during the first ($n = 3$), second ($n = 7$), third ($n = 11$), fourth ($n = 16$), and fifth ($n = 21$) year of ADV treatment. Urinary RBP abnormalities were observed in patients during the first ($n = 2$), second ($n = 8$), third ($n = 12$), fourth ($n = 15$), and fifth ($n = 22$) year of ADV treatment. eGFR decreased 20%-30% from baseline in 20 patients, 30%-50% in 12 patients, and > 50% in 3 patients during the five years of treatment. Further analysis indicated that decreases in eGFR of $\geq 30\%$ relative to the baseline level correlated significantly with urine RBP and β 2-M abnormalities. In contrast, both serum creatinine and eGFR remained stable in patients treated with entecavir, and only one of these patients developed a urine β 2-M abnormality, and two developed urine RBP abnormalities during the five years of treatment.

CONCLUSION: Urine RBP and β 2-M are biomarkers of renal injury during long-term ADV treatment for chronic hepatitis B, and indicate when treatment should be switched to entecavir.

Key words: Adefovir dipivoxil; Entecavir; Retinol binding protein; Renal impairment; Urine β 2-microglobulin

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Abstract

AIM: To evaluate urine β 2-microglobulin (β 2-M), retinol-

Core tip: Identifying a reliable and sensitive biomarker of early renal dysfunction would be helpful for facilitating early intervention and evaluating the effectiveness of treatments for chronic hepatitis B. Urinary β 2-microglobulin and retinol-binding protein are early markers of nephrotoxicity induced by nephrotoxic substances, cardiac surgery, diabetes mellitus, or hypertension. This study shows that long-term adefovir dipivoxil therapy in patients with chronic hepatitis B results in renal impairment that correlates with abnormalities in these markers.

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INTRODUCTION

More than 350 million people worldwide are infected with the hepatitis B virus (HBV)^[1]. Hepatitis B is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma, for which high levels of HBV DNA are an independent factor^[2]. Therefore, the main goal of treatment is complete suppression of HBV replication to limit progressive liver damage and improve the natural history of chronic hepatitis B (CHB). Currently, oral nucleoside analogs have demonstrated success in suppressing virus replication, with few side effects. Evidence-based medicine has demonstrated that a slow virologic response after initiation of nucleoside analog treatment is associated with high rates of long-term drug resistance^[3,4].

Among the available nucleoside analogs, adefovir dipivoxil (ADV) is a phosphonate acyclic nucleotide analog of AMP. It is a potent inhibitor of HBV reverse transcriptase and is effective for patients with hepatitis B e antigen (HBeAg)-positive and HBeAg-negative CHB^[5,6]. ADV also shows no cross-resistance with other nucleoside analogs such as lamivudine (LAM), telbivudine, and entecavir (ETV), and thus is widely used as a rescue therapy for these drugs^[7,8]. However, renal dysfunction associated with prolonged use of ADV has been reported recently^[9-11]. For example, in a study of 10 mg ADV combined with 100 mg LAM, serum creatinine increased in 38% of patients following median treatment duration of 38 mo^[12]. However, most routine renal function tests used in these studies were based on serum creatinine, blood urea nitrogen, and estimated glomerular filtration rate (eGFR), which failed to identify early stages of renal dysfunction and structural injury. Therefore, identification of a reliable and sensitive biomarker of early renal dysfunction would be helpful for facilitating early intervention and

evaluating its effectiveness in CHB patients.

β 2-Microglobulin (β 2-M) is an 11.8-kDa protein, and is a light chain of major histocompatibility class I expressed on the surface of every nucleated cell^[13]. Retinol-binding protein (RBP) is a protein of 21 kDa that is synthesized by the liver. Both β 2-M and RBP are subject to glomerular filtration, the bulk of which undergo proximal tubular reabsorption and catabolism, which might be disrupted in renal dysfunction^[14]. β 2-M and RBP excretion in urine has been reported as an early marker of nephrotoxicity induced by nephrotoxic substances, cardiac surgery, diabetes mellitus, or hypertension^[15]. At present, it remains unclear whether urine β 2-M and RBP can be used as early markers to diagnose renal impairment in CHB patients with long-term ADV treatment. In this study, we aimed to evaluate the relationship between urine β 2-M and RBP excretion and early renal impairment during long-term ADV treatment in CHB patients.

MATERIALS AND METHODS

Patients

From January 2007 to March 2010, 165 patients diagnosed with CHB at the First Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China) were treated with ADV monotherapy ($n = 90$) or ADV and LAM combination therapy ($n = 75$). An additional 165 CHB patients treated with ETV were also recruited as controls. All the patients had normal renal function at the outset of ADV and ETV treatment (serum creatinine $< 59 \mu\text{mol/L}$ and eGFR of $\geq 50 \text{ mL/min per } 1.73 \text{ m}^2$). Urinary excretion of β 2-M and RBP was not detected in any of the patients at the beginning of the study. We excluded patients infected with hepatitis delta virus, hepatitis C virus, or those who had HIV co-infection. Patients with hypertension, diabetes mellitus, hepatocellular carcinoma, autoimmune hepatitis, alcoholic liver cirrhosis, or severe heart, renal and brain diseases were also excluded. All patients who participated in this study provided informed consent and were aware of the procedures to be conducted. The protocol was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University.

Follow-up studies

Serum HBV markers, including hepatitis B surface antigen, anti-HBs, HBeAg, hepatitis B e antibody (anti-HBe), and hepatitis B core antibody, were detected by commercially available enzyme immunoassays (Abbott Laboratories, Chicago, IL, United States). Serum HBV DNA was measured by PCR with a linear range between 1×10^3 copies/mL and 5×10^8 copies/mL (Shanghai ZJ Bio-Tech Co. Ltd., China).

Patients visited our hospital every 3-6 mo after the start of ADV and ETV treatment. Follow-up clinical assessments included physical examination, HBeAg and anti-HBe, quantitative HBV DNA, serum biochemistry, α -fetoprotein, renal function, and

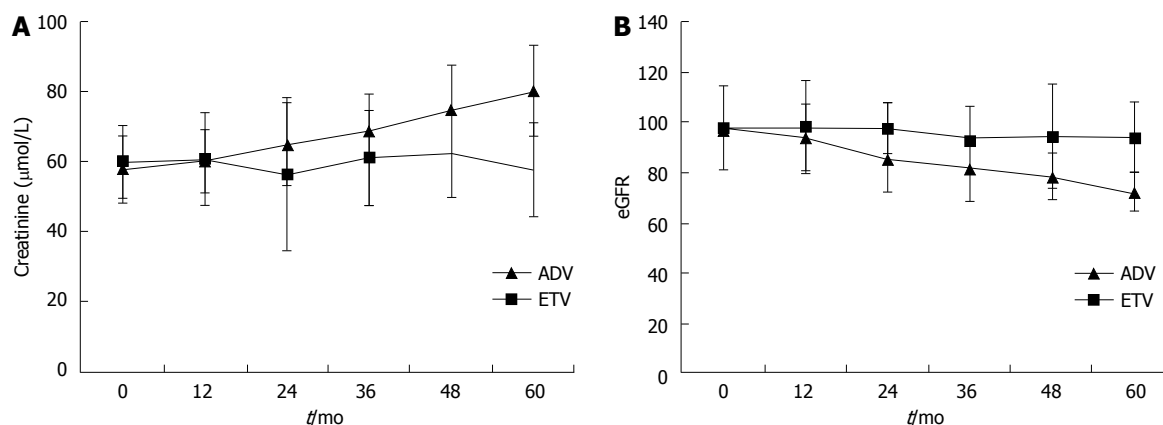


Figure 1 Time course after treatment with adefovir dipivoxil with or without lamivudine and entecavir for chronic hepatitis B patients. A: Changes in mean creatinine level; B: Mean estimated glomerular filtration rate (eGFR) with adefovir dipivoxil (ADV) and entecavir (ETV) administration.

Table 1 Baseline characteristics <i>n</i> (%)			
Characteristic	ADV or ADV + LAM (<i>n</i> = 165)	ETV (<i>n</i> = 165)	<i>P</i> value
Age (yr)	46.2 ± 9.2	48.6 ± 8.7	0.89
Male	115 (69.7)	120 (72.7)	0.68
Treatment duration (mo)	54.6 (12–95)	53.8 (12–98)	0.76
HBeAg positive	95 (57.6)	93 (56.3)	0.64
HBV DNA (log10 copies/mL)	6.65 ± 0.93	6.54 ± 0.89	0.88
Total bilirubin (mmol/L)	48.9 (23–71)	45.7 (21–75)	0.76
ALT (U/L)	146 (85–210)	156 (89–216)	0.54
Albumin (g/L)	45.6 ± 6.7	44.9 ± 7.1	0.32
Creatinine (mmol/L)	57.8 ± 4.6	59.7 ± 8.3	0.45
eGFR (mL/min per 1.73 m ²)	97.8 ± 10.7	96.7 ± 13.5	0.23
Inorganic phosphate (mmol/L)	1.43 ± 0.9	1.37 ± 0.8	0.12
β2-M (g/mol Cr)	1.4 ± 0.006	1.3 ± 0.005	0.55
RBP (g/mol Cr)	1.6 ± 0.004	1.7 ± 0.008	0.51

ADV: Adefovir dipivoxil; ALT: Alanine aminotransferase; β2-M: β2-microglobulin; eGFR: Estimated glomerular filtration rate; ETV: Entecavir; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; LAM: Lamivudine; RBP: retinol-binding protein.

ultrasonography or CT. The eGFR (measured as mL/min per 1.73 m²) was calculated by the Chinese equation [$175 \times \text{Pcr}^{-1.234} \times \text{age}^{0.179}$ (female $\times 0.79$)]. Renal impairment was indicated by a decrease in eGFR to < 50 mL/min per 1.73 m². Urine β2-M and RBP were tested in the First Affiliated Hospital of Zhejiang University. The normal values of urine β2-M and RBP were 0.000–0.025 g/mol Cr, respectively.

Statistical analysis

SPSS version 16.0 software (SPSS Inc., Chicago, IL, United States) was used for data analysis. Measurements are presented as mean ± SD and comparisons were conducted using the Student’s *t* test. Proportions are presented as percentages, and rate comparisons were performed using the χ^2 test. The cumulative incidence of renal impairment and urine β2-M and RBP changes were calculated using the Kaplan-Meier method, and group data were calculated

using the log rank test. The Cox proportional hazard regression model was used to estimate univariate and multivariate risk factors for urine microprotein (β2-M and RBP) abnormalities. *P* < 0.05 was considered significant.

RESULTS

ADV-related nephrotoxicity

Baseline characteristics of the groups did not differ, and are presented in Table 1. Figure 1 shows the dynamic changes in the mean value of creatinine and eGFR from baseline during ADV (with or without LAM) and ETV treatment. The creatinine level increased gradually from the second year, and was increased 20%–30% from baseline in 32/165 (19.4%) patients, 30%–50% in 15/165 (9.1%), and > 50% in 4/165 (2.4%) patients during the five-year period. Serum creatinine was > 104 μmol/L in 5/165 (3.0%) patients treated with ADV. eGFR decreased 20%–30% from baseline in 20/165 (12.1%) patients, 30%–50% in 12/165 (7.2%), and > 50% in 3/165 (1.8%) in patients treated with ADV, and three patients displayed renal impairment (eGFR < 50 mL/min per 1.73 m²). In the ETV control treatment group, both creatinine and eGFR remained stable over the five-year period.

Frequency of urine β2-M abnormality

Cumulative incidences of urine microprotein abnormalities are shown in Figure 2. Urine β2-M abnormality developed in 3/165 (1.8%), 7/165 (4.2%), 11/165 (6.7%), 16/165 (9.7%), and 21/165 (12.7%) patients in the first, second, third, fourth, and fifth year of ADV or ADV plus LAM treatment, respectively. Urine RBP abnormality developed in 2/165 (1.2%), 8/165 (4.8%), 12/165 (1.8%), 15/165 (9.1%), and 22/165 (13.3%) patients in the first, second, third, fourth, and fifth year of treatment, respectively. Only 1/165 (0.1%) patient developed a urine β2-M abnormality, and 2/165 (1.2%) patients developed urine RBP abnormalities during the five years of ETV treatment. The incidence

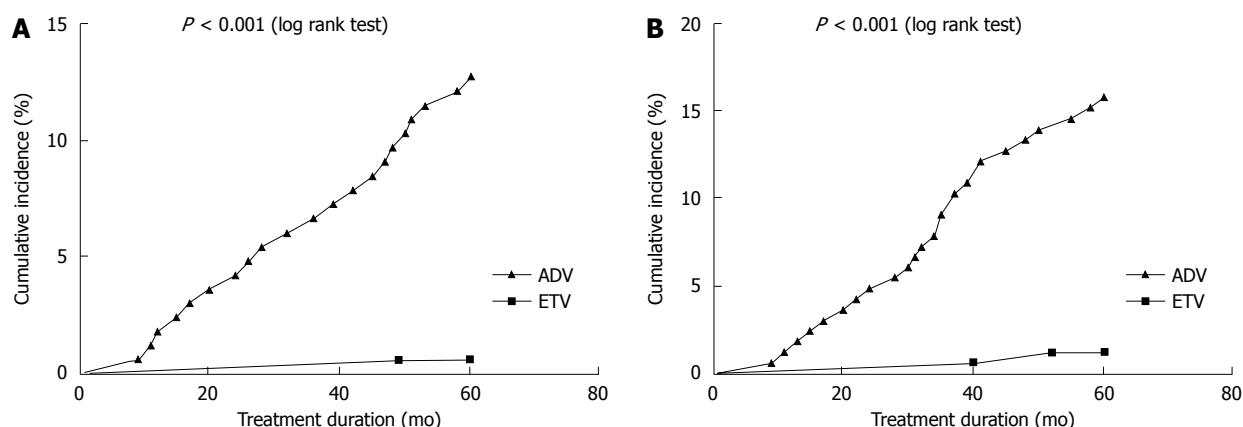


Figure 2 Cumulative incidence of urine microprotein abnormalities after treatment with adefovir dipivoxil with or without lamivudine or entecavir in chronic hepatitis B patients. Cumulative incidence of A: Urine β 2-microglobulin abnormality; and B: Retinol-binding protein abnormality with long-term adefovir dipivoxil (ADV) or entecavir (ETV) treatment.

Table 2 Determinants of urine β 2-microglobulin abnormality

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age \geq 50 yr	5.237 (2.687-10.742)	< 0.001	3.675 (1.612-7.865)	0.003
Male	1.523 (0.876-3.487)	0.782	-	-
Body weight	1.323 (0.712-3.237)	0.574	-	-
Baseline eGFR < 80 mL/min per 1.73 m ²	3.879 (1.657-7.986)	0.001	-	-
ADV treatment	5.178 (2.358-9.867)	< 0.001	3.078 (1.328-6.871)	0.005

ADV: Adefovir dipivoxil; CI: Confidence interval; eGFR: Estimated glomerular filtration rate; HR: Hazard ratio.

of urine β 2-M abnormality in the ADV treatment group was higher than that in the ETV group ($P < 0.001$).

Further analysis indicated that a \geq 30% decrease in eGFR relative to the baseline level after five years correlated significantly with urine RBP and β 2-M abnormality ($P = 0.006$ and 0.005 , respectively).

Predictive factors for urine β 2-M abnormality

The results of univariate and multivariate analyses are indicated in Table 2. Univariate analysis showed that old age (\geq 50 years), ADV treatment, and baseline mild renal dysfunction (eGFR < 80 mL/min per 1.73 m²) were associated with the development of urine β 2-M abnormality (all $P < 0.001$). Multivariate analysis indicated that old age ($P = 0.003$) and ADV treatment ($P = 0.005$) were significant predictors of urine β 2-M abnormality.

Effect of switching ADV to ETV treatment on renal impairment

Among 22 patients with urine β 2-M abnormalities, 11 switched to ETV treatment while the other 11 continued ADV treatment. As indicated in Figure 3, both urine RBP and β 2-M decreased gradually after

switching to ETV treatment for 48 wk, while both urine RBP and β 2-M increased gradually in the ADV or ADV plus LAM treatment group. eGFR increased from 78.5 ± 11.8 mL/min per 1.73 m² to 89.5 ± 13.7 mL/min per 1.73 m² after switching to ETV treatment for 48 wk. eGFR deteriorated from 79.8 ± 14.3 mL/min per 1.73 m² to 68.5 ± 14.3 mL/min per 1.73 m² if ADV was continuously applied.

DISCUSSION

Renal dysfunction is one of the serious adverse effects of ADV. In a previous retrospective study of 687 patients, during a median treatment duration of 27 mo, 10.5% of patients developed renal impairment, which was defined as a decrease in eGFR > 20% relative to baseline^[16]. In another study of 292 patients treated with ADV plus LAM combination therapy, 9.6% patients developed renal impairment during a median treatment duration of 64.3 mo^[9]. Our results show that during the five years of ADV or ADV plus LAM treatment, creatinine increased by 20%-30% from baseline in 19.4%, 30%-50% in 9.1%, and > 50% in 2.4% of patients, while the eGFR decreased 20%-30% from baseline in 12.1%, 30%-50% in 7.2%, and > 50% in 1.8% of patients. Furthermore, five patients had serum creatinine > 104 μ mol/L and three had eGFR < 50 mL/min per 1.73 m² during the five years of ADV or ADV plus LAM treatment. These rates are less than those reported previously, because all the CHB patients with hypertension, diabetes mellitus, and liver cirrhosis were excluded from our study. In contrast to ADV treatment, both creatinine and eGFR remained stable in the ETV treatment group.

Routine renal function tests based on serum creatinine and blood urea nitrogen fail to identify early stages of renal dysfunction and structural injury. Creatinine change is not specific because it can also occur in non-renal disease, reflecting changes in muscle mass and nutrition intake^[17]. eGFR mainly reflects the renal filtration capacity, and cannot detect

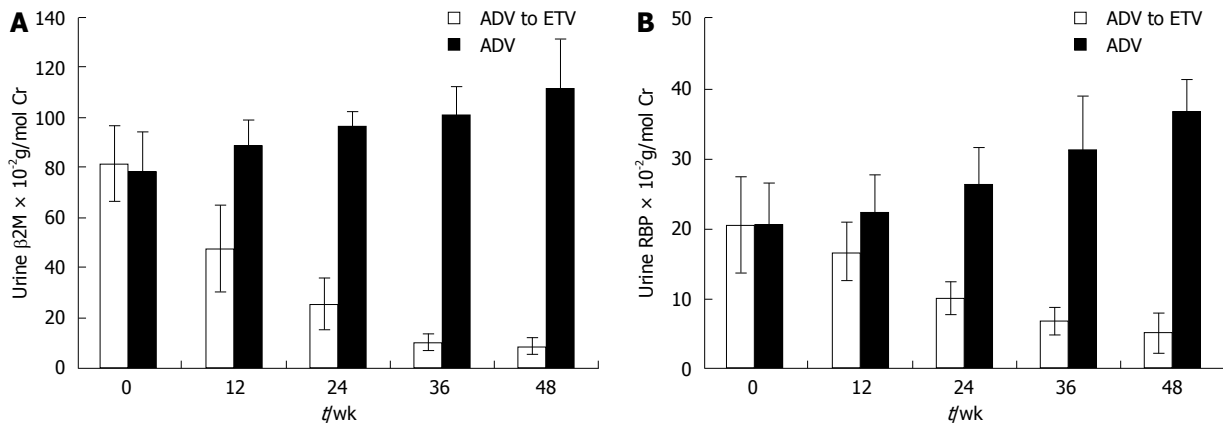


Figure 3 Changes in urine microproteins after modification of adefovir dipivoxil treatment in chronic hepatitis B patients. A: Mean urine $\beta 2$ -microglobulin ($\beta 2\text{-M}$); B: Mean urine retinol-binding protein (RBP) after switching to entecavir treatment [adefovir dipivoxil (ADV) to entecavir (ETV)] or with continued ADV treatment.

the early stage of renal tubular disorders. Therefore, other biomarkers have been examined, such as $\beta 2\text{-M}$, RBP, kidney injury molecule-1, neutrophil gelatinase associated lipocalin, interleukin-18, and sodium/hydrogen exchange form 3^[18]. These biomarkers show increased levels in the urine at an early stage after renal dysfunction occurs. Our results indicate that 1.8%, 4.2%, 6.7%, 9.7% and 12.7% of patients developed urine $\beta 2\text{-M}$ abnormalities, and 1.2%, 1.8%, 4.8%, 9.1%, and 13.3% of patients developed urine RBP abnormalities in the first, second, third, fourth, and fifth year of treatment, respectively. Only 3% of patients displayed serum creatinine $> 104 \mu\text{mol/L}$ and 1.8% eGFR $< 50 \text{ mL/min per } 1.73 \text{ m}^2$ at the same time. This indicates that the urine $\beta 2\text{-M}$ and RBP abnormalities preceded creatinine abnormality renal impairment.

The mechanism of ADV-induced nephrotoxicity may be related to drug accumulation in renal proximal tubules after long-term administration, which may reduce the reabsorption capacity of microproteins ($\beta 2\text{-M}$ and RBP), amino acids, glucose, phosphorus, and calcium^[19,20]. Detection of these biomarkers in serum or urine might be important, because at this stage, positive results should raise awareness of the risk of renal damage at the moment when it is still reversible with prophylactic or therapeutic intervention. In our study, among 11 patients with urine $\beta 2\text{-M}$ abnormality, urine RBP and $\beta 2\text{-M}$ decreased gradually, and eGFR increased after switching to ETV treatment for 48 wk, whereas urine RBP and $\beta 2\text{-M}$ continued to increase, and the eGFR decreased in those remaining on ADV treatment. Our results strongly suggest that ADV should be switched to ETV treatment immediately if urine RBP or $\beta 2\text{-M}$ is detected in CHB patients.

We also analyzed the risk factors of urine $\beta 2\text{-M}$ abnormality after long-term ADV treatment. Consistent with previous reports, our univariate analysis indicated that age was a significant and independent factor of urine $\beta 2\text{-M}$ abnormality, together with long-term ADV administration and baseline mild dysfunction (eGFR

$< 80 \text{ mL/min per } 1.73 \text{ m}^2$)^[9,10]. Multivariate analysis suggested that age and ADV administration were independent factors of urine $\beta 2\text{-M}$ abnormality.

In conclusion, both urine RBP and $\beta 2\text{-M}$ are sensitive biomarkers for detecting early renal injury during long-term ADV treatment. Therefore, when RBP or $\beta 2\text{-M}$ are detected in urine, ADV should be switched to ETV immediately. Moreover, ADV should be avoided as a first-line treatment for CHB patients, especially for elderly people.

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Ding F is a graduate student, now working in the Sixth People's Hospital of Shaoxing, Zhejiang, China.

COMMENTS

Background

Renal dysfunction associated with prolonged use of adefovir dipivoxil (ADV) has been reported recently. However, most routine renal function tests used in these studies were based on serum creatinine, blood urea nitrogen, and estimated glomerular filtration rate (eGFR), which fail to identify early stages of renal dysfunction and structural injury. Therefore, identification of a reliable and sensitive biomarker of early renal dysfunction would be helpful in facilitating early intervention and evaluating its effectiveness for chronic hepatitis B (CHB) patients. The aim of this study was to evaluate the relationship between urine $\beta 2$ -microglobulin ($\beta 2\text{-M}$) and retinol-binding protein (RBP) excretion and early renal impairment during long-term ADV in CHB patients.

Research frontiers

$\beta 2\text{-M}$ is an 11.8-kDa protein, and is a light chain of major histocompatibility class I expressed on the surface of every nucleated cell. RBP is a protein of 21 kDa that is synthesized by the liver. Both $\beta 2\text{-M}$ and RBP are subject to glomerular filtration, and undergo proximal tubular reabsorption and catabolism, which might be disrupted in renal dysfunction. $\beta 2\text{-M}$ and RBP excretion in urine has been reported as an early marker of nephrotoxicity induced by nephrotoxic substances, cardiac surgery, diabetes mellitus, or hypertension. At present, it remains unclear whether urine $\beta 2\text{-M}$ and RBP can be used as early markers to diagnose renal impairment in CHB patients with long-term ADV treatment.

Innovations and breakthroughs

Routine renal function tests based on serum creatinine and blood urea nitrogen fail to identify early stages of renal dysfunction and structural injury. Recently, several biomarkers have been found, such as $\beta 2\text{-M}$, RBP, kidney injury molecule-1, neutrophil gelatinase associated lipocalin, interleukin-18, and sodium/hydrogen exchange form 3, which show increased levels in the

urine at an early stage after renal dysfunction occurs. These results indicated that a proportion of patients developed urine β -M and RBP abnormalities during long-term ADV treatment, which occur before creatinine abnormality and impaired eGFR. Thus, detection of urine β -M and RBP can help identify early renal dysfunction during long-term ADV treatment.

Applications

The study results suggest that urine β -M and RBP can be used as early biomarkers to indicate renal dysfunction during long-term ADV treatment.

Terminology

ADV is a phosphonate acyclic nucleotide analog of AMP. It is a potent inhibitor of hepatitis B virus reverse transcriptase and is effective for patients with chronic hepatitis B infections.

Peer-review

This is a good descriptive study in which the authors analyzed the β -M and RBP excretion induced by long-term ADV treatment in the CHB patients. The results are interesting and suggest that urine RBP and β -M are sensitive biomarkers of early renal injury during long-term ADV treatment. ADV should be switched to ETV as soon as urine RBP or β -M is detected. ADV should be avoided as first-line treatment for CHB.

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