

# Clinical features and risk factors of creatine kinase elevations and myopathy associated with telbivudine

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**SUMMARY.** With the extensive use of telbivudine, more and more studies reported its association with creatine kinase (CK) elevations and myopathy. However, clinical features of these adverse effects were poorly understood. The aim of the present study was to investigate the clinical features and risk factors of CK elevations and myopathy associated with telbivudine. The serum CK levels of 200 patients who were treated with telbivudine for chronic hepatitis B (CHB) between January 2007 and July 2010 were monitored and analysed along with clinical manifestations. The 3-year cumulative incidence of CK elevations and myopathy was 84.3% and 5%, respectively. CK elevations occurred more frequently in men than in women, and patients aged  $\leq 45$  years and with negative HBeAg had higher incidence of CK elevations. There was no difference in CK elevations among patients with different HBV DNA levels. Male,

younger age and HBeAg negativity were independent predictors of CK elevations by multivariate Cox regression analysis. There was no association between the occurrence of myopathy and variables including age, sex, HBeAg and HBV DNA. No risk factors of myopathy were identified. CK elevations usually occurred 21 months after starting treatment, and most patients resolved spontaneously without interruption of telbivudine therapy except three patients who had to switch to other agents. In conclusion, CK elevations are common adverse reactions associated with telbivudine therapy, while myopathy is rare. Male, younger age and HBeAg negativity might be risk factors of CK elevations.

**Keywords:** creatine kinase elevation, hepatitis B virus, myopathy, myositis, rhabdomyolysis, telbivudine.

## INTRODUCTION

Telbivudine is a new synthetic nucleoside analogue licensed in October 2006. Compared with lamivudine, telbivudine has a lower drug resistance rate and higher rates of virological response, HBeAg seroconversion and ALT normalization [1]. Because of its high activity in achieving sustained suppression of hepatitis B virus replication (HBV), it is a new option for the treatment of chronic hepatitis B (CHB). Telbivudine has been reported to be associated with creatine kinase (CK) elevations and myopathy, which was the same as other nucleoside analogues like lamivudine and clevudine [2–4]. It is noteworthy that a case with rhabdomyolysis

caused by telbivudine has been reported [5]. The State Food and Drug Administration of China had drawn public attention to the safety alert issued on 22 July 2010 regarding the risk of rhabdomyolysis associated with the use of preparations containing lamivudine and telbivudine.

However, there has been no overall report about telbivudine-related adverse reactions to date, except in its registration clinical trials. Almost all reports just mentioned the incidence of CK elevations and myopathy associated with telbivudine. Seldom studies considered the clinical features and risk factors of these adverse reactions. Zhang *et al.* [6] proposed that combination therapy with interferon or another nucleoside analogue and a high dose might increase the risk of severe adverse reactions, but this needs to be confirmed by increasing the number of observed cases because there were only five patients with severe adverse reactions in the study.

The aim of the present study was to investigate the clinical features and risk factors of CK elevations and myopathy associated with telbivudine and provide a more theoretical basis for clinicians in preventing and treating adverse reactions during telbivudine therapy.

Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; CHB, chronic hepatitis B; CI, confidence interval; CK, creatine kinase; HBV, hepatitis B virus; RR, relative risk; SD, standard deviation; ULN, upper limit of normal.

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## MATERIALS AND METHODS

### Patients

The study was conducted between January 2007 and July 2010 at Tongji Hospital. All patients were categorized as chronic HBV carriers according to EASL clinical practice guidelines [7].

### Methods

All patients were treated with 600 mg of telbivudine once daily and told not to do high-intensity, long-duration and weight-bearing exercise during therapy. The median duration of telbivudine therapy was 24 months (range 12–42 months). Serological markers of HBV infection were tested for using commercially available microparticle enzyme immunoassay kits (AxSYM; Abbott Laboratories, Abbott Park, IL, USA). HBV DNA was detected and quantified by a commercial real-time PCR assay (DaAn Gene Co. Ltd, Guangzhou, China). In the course of treatment, serum CK levels were detected by an automatic biochemistry analyser (Hitachi 7600; Hitachi Co., Tokyo, Japan) using commercial CK assay kits (Roche Diagnostics, Mannheim, Germany) every 3 months. Adverse reactions were observed at the same time.

### Evaluation of the results

Values of CK >191 U/L and >171 U/L, respectively, in male and female patients were regarded as elevated. Referring to the GLOBE study [8], the levels of CK elevation were divided into 4 grades: values of CK 1–3 times the upper limit of normal (ULN), 3–7 ULN, 7–10 ULN and >10 ULN were, respectively, defined as grade 1, grade 2, grade 3 and grade 4 CK elevations.

Myopathy included muscle symptoms, myositis and rhabdomyolysis according to severity. Muscle symptoms included mainly muscle pain or weakness with normal or slightly elevated CK. Myositis patients not only suffered from muscle symptoms but also had CK elevations (3–10 ULN). Rhabdomyolysis patients had muscle symptoms with significantly increased CK levels (>10 ULN), accompanied by increased serum creatinine and myoglobinuria [9].

### Statistical analysis

Statistical analysis was carried out using the Statistical Package for Social Science (SPSS version 13.0 for Windows; SPSS Inc., Chicago, IL, USA). Descriptive statistics for continuous variables included mean  $\pm$  SD as well as median (range). A Kaplan–Meier curve was plotted to depict the incidence of CK elevations and myopathy, and the log-rank test was used to compare the incidence among the groups. Occurrence of CK elevations and

myopathy were considered as dependent variables, and variables like age, sex, HBeAg and HBV DNA were considered as independent variables. Among these independent variables, sex and HBeAg were considered as categorical variables and the remaining were continuous variables. A univariate Cox proportional hazard regression was performed to calculate unadjusted relative risk (RR) with its 95% confidence interval (CI). Subsequently, a multivariate Cox proportional hazard regression was performed to identify the adjusted RR and the CI of the independent variables for occurrence of CK elevations and myopathy among the patients.

## RESULTS

### General information

The mean age of the 200 enrolled patients (men 150, women 50) was 32.1 years (SD = 11.1, range 16–65 years). One hundred and forty-two patients were HBeAg positive and the others were HBeAg negative.

### Status of creatine kinase elevations and myopathy

During the study period, 122 patients had various degrees (grade 1–4) of CK elevations. Among these, elevations in 107 patients were of grade 1/2, and 15 patients had grade 3/4. Symptoms of myopathy were observed in nine patients, while in five patients, these were accompanied by CK elevations ( $>3 \times$  ULN). These were finally diagnosed with myositis following an electromyogram (Table 1).

Creatine kinase elevations appeared between 2 and 36 months after the initiation of therapy in the 122 patients,

**Table 1** Baseline characteristics of patients and the status of CK elevations and myopathy

Variable	Status n (%)
Number of patients	200
Duration of telbivudine therapy [medium (range)] (months)	24 (12–42)
Age (mean $\pm$ SD) (years)	32.1 $\pm$ 11.1
Male gender	150 (75)
HBeAg positive	142 (71)
Number of patients with CK elevations	122
Grade 1 (1–3 $\times$ ULN)	77 (63.12)
Grade 2 (3–7 $\times$ ULN)	30 (24.59)
Grade 3 (7–10 $\times$ ULN)	9 (7.37)
Grade 4 ( $>10 \times$ ULN)	6 (4.92)
Number of patients with myopathy	9
Muscle symptoms	4 (44.44)
Myositis	5 (55.56)
Rhabdomyolysis	0 (0)

and the median time was 21 months. The 3-year cumulative incidence of CK elevations was  $84.3 \pm 6\%$ .

Myopathy occurred between 6–22 months after treatment, and the 3-year cumulative incidence of myopathy was  $5\% \pm 1.7\%$ .

#### *Clinical features of creatine kinase elevations and myopathy associated with telbivudine*

CK elevations were found in 102 male and 20 female patients. The mean age of these patients was 31.96 years (SD = 12.37, range 18–65 years). Nine patients with myopathy were all men and middle aged (mean age 33.33 years, SD = 13.36, range 20–65 years).

Creatine kinase elevations occurred more frequently in men than in women ( $P = 0.007$ ). Compared to patients aged  $\geq 45$  years, patients aged  $\leq 45$  years had higher incidence of CK elevations (all with  $P < 0.05$ ). The incidence of CK elevations in HBeAg-negative patients was significantly higher than that in HBeAg-positive patients ( $P = 0.012$ ). There was no significant difference among the three HBV DNA groups (all with  $P > 0.05$ ; Table 2).

As for the incidence of myopathy, there were no differences in patients with sex, age, HBeAg and HBV DNA status (all with  $P > 0.05$ ; Table 2).

#### *Risk factors of creatine kinase elevation and myopathy associated with telbivudine*

Multivariate analysis revealed that male (RR 1.83, 95% CI 1.13–2.96), younger age (RR 0.97, 95% CI 0.95–0.99) and HBeAg negativity (RR 1.81, 95% CI 1.24–2.66) were independent predictors of CK elevations (Table 3). No independent predictors of myopathy were identified by multivariate analysis.

#### *Treatment and prognosis*

Asymptomatic patients or patients with CK elevations grade 3 or lower did not receive any special intervention. CK resolved to normal or only slightly higher than normal after 3–6 months of observation.

Fifteen patients with grade 3/4 of CK elevations and nine patients with myopathic symptoms were treated with coenzyme Q10, vitamin B1 and vitamin B12 without interruption of telbivudine therapy. Most patients resolved after 1–2 months of these treatments. However, symptoms were not relieved and serum CK levels continued to rise in three patients of 200, so they had to switch to adefovir for antiviral treatment, and all of them recovered 3 months later. None of them progressed to rhabdomyolysis.

**Table 2** Clinical features for CK elevations and myopathy associated with telbivudine

Variable	Overall	CK elevation		Myopathy	
		<i>n</i>	3-year cumulative incidence $\pm$ SD (%)	<i>n</i>	3-year cumulative incidence $\pm$ SD (%)
Number of patients	200	122		9	
Sex					
Male	150	102	$86.3 \pm 4.9^*$	9	$6.6 \pm 2.2$
Female	50	20	$72.6 \pm 20.5$	0	
Age (years)					
16–25	61	43	$79.6 \pm 7.5^{\#}$	1	$1.6 \pm 1.6$
26–35	64	37	$81.7 \pm 8.5^{\#}$	4	$6.2 \pm 3.0$
36–45	50	34	$91.4 \pm 7.5^{\#}$	3	$6.2 \pm 3.5$
46–55	25	4	$33.3 \pm 14.9$	0	
56–65	10	4	$45.0 \pm 15.8$	1	$14.3 \pm 13.2$
HBeAg					
Positive	142	78	$85.9 \pm 10.5$	7	$5.2 \pm 1.9$
Negative	58	44	$89.2 \pm 5.9^{\dagger}$	2	$4.1 \pm 2.9$
HBV DNA					
$\leq 10^4$ copies/mL	25	15	$81.2 \pm 14.4$	1	$4.0 \pm 3.9$
$10^5$ – $10^6$ copies/mL	86	63	$86.1 \pm 6.2$	4	$5.6 \pm 2.8$
$\geq 10^7$ copies/mL	89	44	$74.3 \pm 9.1$	4	$4.5 \pm 2.2$

CK, creatine kinase; HBeAg, Hepatitis B e antigen; HBV, hepatitis B virus.

\* $P < 0.05$  vs female by log-rank test;  $^{\#}P < 0.05$  vs age 46–55 and 56–65 years groups by log-rank test;  $^{\dagger}P < 0.05$  vs HBeAg-positive group by log-rank test.

**Table 3** Risk factors for CK elevations and myopathy associated with telbivudine by the Cox proportional hazard model

Variables	Categories	CK elevation		Myopathy	
		Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Sex	Female	1		1	
	Male	1.83 (1.14–2.96)	1.83 (1.13–2.96)	31.36 (0.05–19911.17)	
HBeAg	Positive	1		1	
	Negative	1.55 (1.07–2.23)	1.81 (1.24–2.66)	0.64 (0.13–3.10)	
Age	Continuous	0.98 (0.96–1)	0.97 (0.95–0.99)	1.02 (0.97–1.08)	
HBV DNA	Continuous	0.96 (0.85–1.1)		1 (0.6–1.64)	

## DISCUSSION

Creatine kinase is an enzyme expressed by various tissues and cell types. CK catalyzes the conversion of creatine and utilizes adenosine triphosphate (ATP) to create phosphocreatine and adenosine diphosphate (ADP). Elevation of CK is an indication of muscle damage. It is therefore indicative of injury, rhabdomyolysis, myocardial infarction, muscular dystrophy, myositis, myocarditis, malignant hyperthermia and neuroleptic malignant syndrome. However, using a variety of medications such as statins, nucleoside analogues also can induce CK elevations. This study showed that CK elevations might occur in 84.3% of patients who had been taking telbivudine for 3 years. Fifteen patients experienced grade 3/4 CK elevations. Men were more prone to develop CK elevations than women, and patients aged  $\leq 45$  years had significantly higher incidence of elevated CK values. CK elevations usually occurred 21 months after telbivudine therapy and were mostly asymptomatic and transient. Most patients could resolve spontaneously after 1–2 months of observation without any intervention and continued on telbivudine without any interruption. These results were consistent with the GLOBE study [8,10].

To our knowledge, there has been no report about the predisposing factors of telbivudine-related CK elevations. This is the first report demonstrating that male, younger age and HBeAg negativity were independent predictors of CK elevations. Exercise is known to elevate CK, and we observed a transient, sometimes extremely high level in a few patients who did high-intensity exercise. CK levels decreased without interruption of telbivudine after halting exercise. So, in this study, all patients were told not to do high-intensity, long-duration and weight-bearing exercise. Nevertheless, younger age and being male were identified as independent predictors of CK elevations. This may be related to their (younger men) higher physical strength/work and higher muscle activity in daily life. Wu *et al.* [11] proposed that HBeAg might modify disease progression by inhibiting inflammatory cytokine and IFN gene expression while simultaneously suppressing NF- $\kappa$ B-signalling- and IFN $\beta$ -promoter activation. NF- $\kappa$ B activation following

exercise could induce the expression of acute-phase proteins and proinflammatory genes that may facilitate muscle injury postexercise [12]. So we speculated that HBeAg might decrease muscle damage by suppressing NF- $\kappa$ B activation and inhibiting inflammatory cytokine expression. This may be the reason why HBeAg-negative patients were prone to CK elevations. However, further studies are needed to confirm it.

In recent years, reports about telbivudine-caused myopathy increased annually. The incidence of myopathy symptoms was 2.35% [13], but occurrence of myositis was rare, only 0.3–0.88% [8,14] in clinical trials. Rhabdomyolysis associated with telbivudine has also been reported [5]. In our study, the 3-year cumulative incidence of myopathy was 5%. No cases of rhabdomyolysis were found. Patients with myopathy had various clinical manifestations, including muscle tenderness, muscle weakness and myalgia of different muscles such as the gastrocnemius muscle, pectoralis major and deltoid muscle. By univariate and multivariate Cox proportional hazard regression analysis, variables such as age, sex, HBeAg and HBV DNA were not risk factors for myopathy. However, there were only nine patients who had myopathy in our study, and only four variables were analysed in the study. These factors may have limited the ability of the study to find any differences. Therefore, further studies are needed to clarify this.

Creatine kinase values were only slightly elevated in four patients ( $<3$  ULN) among nine patients with myopathic symptoms, while only three patients had myopathic symptoms among 15 patients whose CK elevations reached grade 3/4. It was indicated that there was no absolute correlation between myopathic symptoms and degree of CK elevations. Although CK elevations may not progress into myopathy, patients with CK grade 3/4 elevations may develop rhabdomyolysis, renal failure and even die from these complications in the absence of timely intervention. So monitoring serum CK level is necessary during telbivudine therapy. Additionally, because CK values in some patients with myopathy were normal, follow-up of myopathic symptoms and signs was equally important. Only this way we can detect severe adverse reactions and intervene earlier.

The mechanism of telbivudine causing CK elevations and myopathy is currently unclear. Some scholars suspect that it is related to mitochondrial toxicity, because other nucleoside analogues such as lamivudine, clevudine and zidovudine could induce mitochondrial damage [15]. But *in vitro* data showed telbivudine was not associated with the inhibition of mammalian DNA polymerase by mitochondrial toxicity [16]. The exact pathogenesis needs to be further studied. Coenzyme Q10 is an activator of cellular metabolism and cellular respiration. It can improve mitochondrial function, promote oxidative phosphorylation and protect the structural integrity of membranes. Coenzyme Q10 has been used to treat statin and zidovudine-related myopathy [17,18]. In our study, coenzyme Q10 was used in patients who were symptomatic or had CK grade 3/4 elevations. We found that all patients improved except for three. This indicated that coenzyme Q10 might be an effective therapy for telbivudine-related myopathy.

In summary, CK elevation is a common adverse reaction associated with telbivudine therapy. It usually occurs 21 months after starting treatment. Most elevations are benign and reversible. Only few patients developed myopathy. Therefore, as long as patients are closely monitored for CK levels, myopathic symptoms and signs during the period of treatment, telbivudine is still a safe antiviral drug. Once patients are diagnosed with myositis, they should be given appropriate treatment immediately to prevent rhabdomyolysis. Using other effective antiviral drugs to replace telbivudine is sometimes necessary.

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