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Telbivudine-Induced Myopathy: Clinical Features, Histopathological Characteristics, and Risk Factors

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Background and Purpose Oral nucleos(t)ide analogs (NAs) are the mainstay treatment for chronic hepatitis B (CHB). Myotoxicity is an important extrahepatic effect related to NA treatment. Telbivudine is the NA for CHB that is frequently associated with muscle-related side effects. The risk factors for telbivudine-induced myopathy (TIM) are not yet clear.

Methods This study characterized the clinical, magnetic resonance images (MRI), and pathological features of 12 TIM cases. A group of telbivudine-tolerant (TT) patients with CHB who received regular telbivudine treatment during the same period without the occurrence of myopathy was collected. Demographic and clinical factors were compared between the patients with TIM and the TT controls. Factors independently associated with TIM were identified using logistic regression analysis.

Results The patients with TIM (males/females: 7/5, mean age: 57 years) developed myopathy after using telbivudine for a median period of 19.5 months. Muscle histopathology revealed abnormal proliferation, subsarcolemmal or sarcoplasmic accumulations, and ultrastructural defects of mitochondria. When compared with TT cases, patients with TIM had a lower estimated glomerular filtration rate and were more frequently positive for hepatitis B e antigen (HBeAg).

Conclusions Mitochondrial abnormalities are characteristic histopathological features, and impaired renal function and HBeAg positivity are risk factors for TIM. Telbivudine-induced mitochondrial dysfunction and immune activation related to mitochondrial damage and HBeAg serostatus changes may underlie TIM. Constant clinical surveillance of myopathy during telbivudine treatment is needed due to the significant latency of its development. Dose adjustment for impaired renal function does not eliminate the risk of TIM occurrence.

Keywords telbivudine; myopathy; mitochondria; hepatitis B e antigen; chronic hepatitis B.

INTRODUCTION

Chronic hepatitis B (CHB) is a major chronic liver disease that affects more than 250 million people worldwide, with 75% of patients residing in the Asia Pacific region.[1] Chronic infection with hepatitis B virus (HBV) is reportedly associated with a 15%–40% risk of developing chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) throughout the lifetime of the patient.[2] Taiwan has a large CHB epidemic, with approximately 2.5 million patients infected with HBV.[3] After the implementation of a nationwide vaccination program for newborns in 1984, the HBV surface antigen (HBsAg) seropositivity rate in children decreased dramatically from 11% to 0.9% by 2012.[4,5] A national viral hepatitis therapy program for chronic HBV infection was implemented through funding from the National Health Insurance program of Taiwan in 2003, and it has expanded the insurance coverage for new therapies over time.[6]

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Two groups of antiviral agents have been approved for CHB treatment: conventional or pegylated interferons (IFNs) and oral nucleos(t)ide analogs (NAs). Because of the disadvantages of IFNs, including severe side effects, liver cirrhosis aggravation, and induction of autoimmune diseases, NAs are currently the mainstay of CHB treatment. NAs suppress viral replication to achieve their therapeutic effects by inhibiting reverse transcriptase or DNA polymerase. Additional NAs have been developed to treat various viral infections. NA therapy reportedly reduced the HCC incidence in Taiwan over 7 years from 22.7% to 7.32% in patients with HBV infection, and reduced the risk of HCC recurrence following tumor resection by 33%.[7,8]

Myotoxicity is an important extrahepatic effect related to NA treatment. Telbivudine is a thymidine analog that was approved by the FDA in 2006 for treating chronic HBV infection. Telbivudine inhibits HBV DNA polymerase by competing with its natural substrate thymidine-5'-triphosphate and impeding HBV replication. Telbivudine is the NA currently used to treat CHB that is most frequently associated with muscle-related side effects. In the phase III worldwide GLOBAL trial, 88 (12.9%) of the 680 patients who received telbivudine developed grade 3 or 4 (>sevenfold higher than the upper limit of normal) elevation in creatine kinase (CK) levels, which was significantly higher than the rate of 4.1% among those who received lamivudine.[9] Most instances of CK elevation were asymptomatic and transient. Only two (0.29%) patients required cessation of NA due to overt myopathy, which is characterized by muscle weakness and myalgia, but not CK elevation. On the other hand, biochemical changes and clinical myopathy presentation seem to be found more often in studies in real-world settings. In a prospective study that specifically investigated muscle-related side effects, the 3-year cumulative incidence of CK elevation was as high as 84.3% among 200 patients treated using telbivudine for a median duration of 21 months.[10] Nine patients (4.5%) experienced myopathy, three of which required discontinuation of telbivudine treatment.

There have been 20 telbivudine-induced myopathy (TIM) cases reported in the literature with detailed descriptions of clinical, imaging, or pathological features.[11-24] Two small case series included three and four patients, but for the others only a single case was reported. Little is currently known about the risk factors for this severe adverse event related to telbivudine treatment. Here we present a case series of TIM, and characterize their notable clinical, magnetic resonance images (MRI), and pathological features. We also conducted a retrospective investigation of the risk factors for TIM. In view of the extensive use of NAs to treat various viral infections and malignancies, this study may provide pertinent information for preventing TIM and other NA side effects.

METHODS

The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No. 201900946B0). Medical records of the participants were reviewed, and their clinical features were examined after obtaining written informed consent.

Patients

The study included 12 patients with TIM diagnosed in the Department of Neurology of Chang Gung Memorial Hospital from January 2012 to December 2016. Myopathy was defined as muscle weakness with or without myalgia, CK elevation, and myopathic patterns on electromyography or muscle MRI. A group of 60 telbivudine-tolerant (TT) patients with CHB was recruited, who had received regular telbivudine treatment for at least 30 months during the same period in the Hepatobiliary Department of the same hospital without the occurrence of muscle weakness or myalgia, and had renal function and serum hepatitis B e antigen (HBeAg) data from the time of telbivudine treatment initiation. Two patients with TIM (cases 4 and 10) received combined telbivudine and adefovir treatment on the development of myopathy. None of the other patients with TIM nor any of the TT patients received combined NA or IFN treatment.

Histopathology of muscle biopsy samples

A muscle biopsy of the vastus lateralis of the quadriceps femoris was performed on 11 patients with TIM. The biopsy was snap frozen in isopentane and cooled using liquid nitrogen, sectioned at 8 μm, and stained with hematoxylin and eosin, modified Gomori trichrome (mGT), nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR), and a standard set of histochemical stains, including myofibrillar ATPase (pH 4.6 and 9.4), Sudan Black B, periodic acid-Schiff (PAS), acid phosphatase, cytochrome c oxidase (COX), and succinate dehydrogenase (SDH). Ultrathin sections were stained with uranyl acetate and lead citrate and examined using electron microscopy (EM). Structural and biochemical changes in muscle histology were interpreted and rated for severity by an experienced myopathologist (S-S Chen).

Statistical analysis

Continuous variables are presented as mean±standard-deviation values except where stated otherwise. The demographic and clinical factors of patients with TIM and TT controls were compared using the χ^2 test (categorical variables) or the *t*-test (continuous variables). Two multivariable logistic

regression models were used to investigate the independence of the factors associated with TIM. The independent variables in Model 1 included age, sex, hypertension, diabetes mellitus, liver cirrhosis, baseline estimated glomerular filtration rate (eGFR),[25] and HBeAg status before telbivudine treatment. The independent variables in Model 2 were the same as in Model 1 except that baseline eGFR was replaced by chronic kidney disease stage for the renal function parameter. A probability value of $p<0.05$ was considered significant.

RESULTS

Clinical characteristics, skeletal muscle MRI, and muscle pathology of patients with TIM

The 12 patients with TIM (males/females=7/5, age 57±11 years) developed muscle symptoms after using telbivudine treatment for a median period of 19.5 (range 10–29) months (Table 1). The telbivudine dosage was 600 mg per day (eGFR ≥40 mL/min/1.73 m^2) in nine cases, 600 mg every 2 days (eGFR <40 mL/min/1.73 m^2) in two cases, and 600 mg weekly for one patient (hemodialysis) according to dosage adjustment based on renal function. Six patients had liver cirrhosis, and seven were positive for serum HBeAg. Peak CK levels were 186–2835 (median 574.5) IU/L. MRI was performed on lower limb skeletal muscle in five patients with TIM (cases 2, 3, 4, 5, and 8). Cases 4 and 5 received telbivudine treatment for 21 and 44 months, respectively, and showed marked hyperintensities in the fascia and muscles in the anterior compartment of the thigh, and mild hyperintensities in the calf muscles on T2-weighted short tau inversion recovery (STIR) images (Fig. 1A and C), which suggested edematous changes. T1-weighted images indicated interstitial hyperintensity in and between the involved muscles, suggesting epimysial and perimysial fat replacement (Fig. 1B). Case 2, who had received telbivudine for 37 months, had only a mild increase in T2-weighted STIR signals in the quadriceps femoris (Fig. 1D). Cases 3 and 5 had normal MRI findings after 21 and 12 months of telbivudine treatment, respectively. There was a general tendency—but no consistent correlation—between the T2-weighted STIR imaging changes and telbivudine treatment duration or peak CK level.

The muscle histopathology findings in the 11 TIM cases are listed in Table 2. Round and angular atrophic muscle fibers with endomysial fibrosis were present in all patients with TIM. A few necrotic and phagocytic fibers were also found (Fig. 2A and B). Mild intrafascicular infiltration of inflam-

Table 1. Clinical information of the patients with TIM

Case no.	Age (years)*	Sex	Liver cirrhosis	CKD stage	HBeAg	Telbivudine dosage (mg)	Time from telbivudine use (months)			Peak CK level (IU/L)
							TIM onset	Muscle biopsy	Total	
1	66	M	+	2	+	600 per day	11	23	22	469
2	56	M	-	2	-	600 per day	22	34	40	977
3	54	F	-	1	-	600 per day	16	20	22	186
4	56	M	-	5	+	600 per week†	21	21	21	436
5	56	M	+	4	+	600 per 2 days	22	42	46	990
6	60	M	+	3	-	600 per 2 days	29	33	34	2,835
7	48	M	-	1	+	600 per day	18	24	24	1,244
8	44	F	-	2	+	600 per day	10	12	12	225
9	56	F	-	2	-	600 per day	27	105	102	267
10	70	F	+	3	+	600 per day†	14	26	25	652
11	77	M	+	3	-	600 per day	11	14	22	612
12	39	F	+	1	+	600 per day	28	-	32	537

*Age at the clinical onset of myopathy; †Combined with adefovir use.
CK, creatine kinase; CKD, chronic kidney disease; F, female; HBeAg, hepatitis B e antigen; M, male; TIM, telbivudine-induced myopathy.

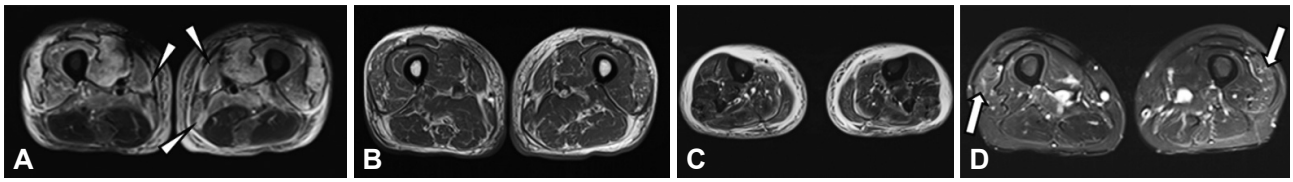

Fig. 1. Lower limb skeletal muscle MRI of telbivudine-induced myopathy. A-D: Case 5 showed diffuse increases in signal intensities in the anterior compartments of thigh muscles (A) and fascia (arrowheads) and, to a lesser extent, in the calf muscles (C) on T2-weighted STIR images, with mottled intramuscular and intermuscular hyperintensity of the affected muscles on T1-weighted images (B). Case 2 showed mild hyperintensities in the bilateral lateral head of quadriceps femoris on T2-weighted STIR image (D, arrows). STIR, short tau inversion recovery.

Table 2. Histopathological features of muscle biopsies from patients with telbivudine-induced myopathy*

Case no.	1	2	3	4	5	6	7	8	9	10	11
Atrophic fibers	+	+	+	+	+	+	+	+	+	+	+
Necrosis/phagocytosis	±	+	+	+	+	-	+	+	-	-	+
Endomysial fibrosis	+	+	+	+	+	+	+	+	+	++	+
Perifascicular fibrosis	-	-	-	-	-	-	-	+	-	+	-
Inflammatory cell infiltration	-	+	-	-	-	-	-	-	-	-	+
Vacuolar fibers (H-E)	++	+	-	±	+	-	+	++	±	+	-
Lipid storage	+	++	+	++	+	-	+	+	-	±	+
Eosinophilic inclusions (mGT)	+	+	+	+	±	-	+	++	±	-	++
SDH activity	+	++	++	+	+	±	±	++	±	+	+
Mitochondrial changes on EM†	+	++	++	+	+	+	+	++	++	±	++

*Severity grading: -, absent; ±, trace; +, mild; ++, marked; †Mitochondrial proliferation and regional accumulation.
EM, electronic microscopy; H-E, hematoxylin and eosin; mGT, modified Gomori trichrome; SDH, succinate dehydrogenase.

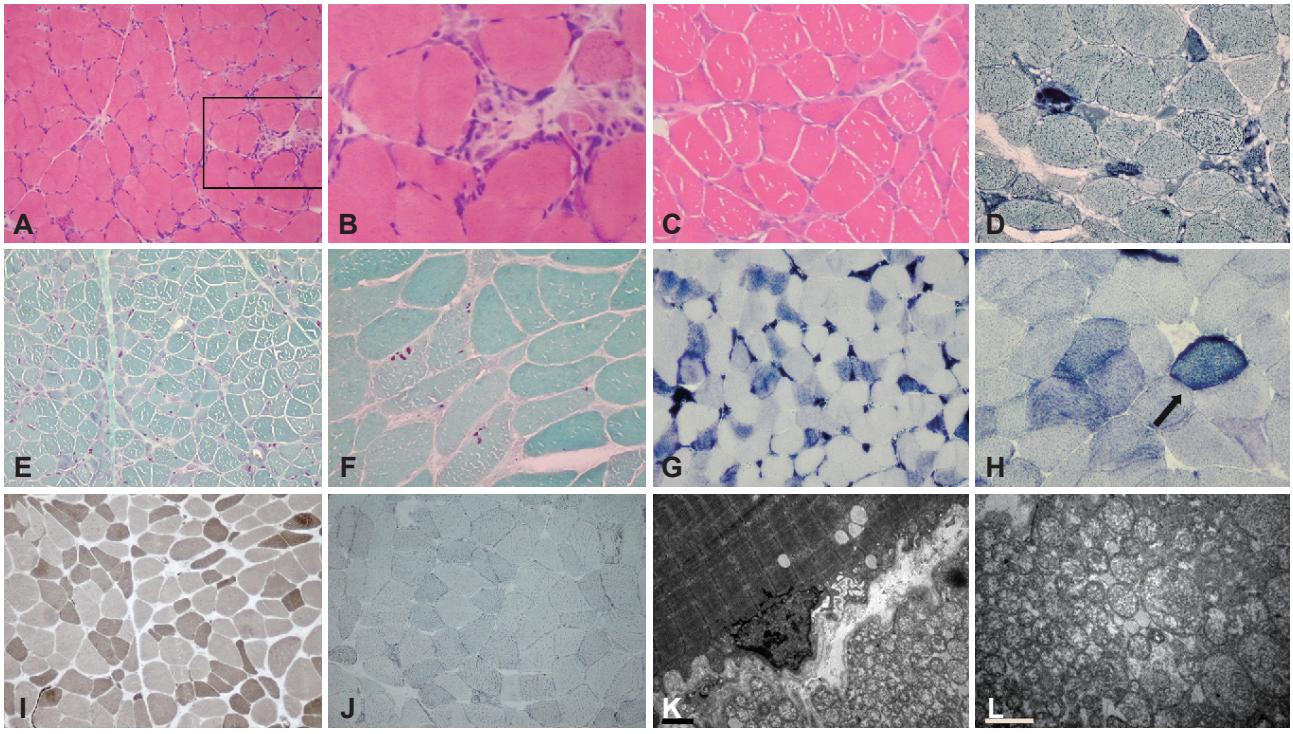

Fig. 2. Muscle histopathological features of telbivudine-induced myopathy. A-L: Histopathology revealed scattered angular or round atrophic fibers (A), and a phagocytic fiber (magnified in B) in the enclosed area; sarcoplasmic vacuoles (C), some stained positive for lipids (D), subsarcolemmal or sarcoplasmic, granular or rod-shaped inclusions (E and F), atrophic fibers positive for succinate dehydrogenase on stains (G), some with the appearance of "ragged-blue fibers" (H, arrow); type 2 fibers predominantly affected by atrophic changes (I), generally normal COX activity (J), mitochondrial proliferation with subsarcolemmal accumulation (K, lower right corner), and homogenized mitochondrial matrix (L). The stains used were hematoxylin and eosin (A-C), Sudan Black B (D), modified Gomori trichrome (E and F), succinate dehydrogenase (G and H), ATPase (pH 9.4) (I), and COX (J), and uranyl acetate and lead citrate in electron microscopy imaging (K and L). Magnifications: ×200 (A, E, G, I, and J), ×400 (C, D, F, and H), ×5000 (K), and ×8000 (L). COX, cytochrome c oxidase.

matory cells was observed in only two patients (cases 2 and 11, 18%). Various proportions of muscle fibers filled with cytoplasmic vacuoles, some of which stained positive for lipids, were noted in eight cases (73%) (Fig. 2C and D). The most distinctive features were red, granular, or rod-shaped subsarcolemmal or sarcoplasmic deposits in the atrophic fibers on mGT staining (Fig. 2E and F), which were present in nine patients (81%). These fibers were also intensely stained with SDH, with diffuse coarse stippling or a "ragged-blue" appearance (Fig. 2G and H), and were positively stained by NADH-TR at their periphery. The aforementioned pathological abnormalities, including atrophy, necrosis, intracellular inclusions, lipid accumulation, and SDH hyperactivity, predominantly affected type 2 fibers (Fig. 2I). COX activity was preserved ex-

Table 3. Univariate analysis of clinical data between TIM patients and TT controls

	TIM	TT	*p*
Case number	10*	60	
Age (yr)†‡	54±11	54±12	0.970
Male sex, *n* (%)	6 (60)	41 (68.3)	0.603
Diabetes mellitus, *n* (%)	3 (30)	9 (15)	0.244
Liver cirrhosis, *n* (%)	5 (50)	38 (63.3)	0.423
CKD stage, *n* (%)			0.406
1	3 (30)	31 (51.7)	
2	4 (40)	22 (36.7)	
3	2 (20)	5 (8.3)	
4	1 (10)	2 (3.3)	
5	0	0	
eGFR (mL/min/1.73 m^2)‡	72.1±27.9	91.7±28.5	0.048
HBeAg positive, *n* (%)	5 (50)	12 (20)	0.041

*Excluding two patients receiving combined telbivudine and adefovir treatment; †Start of telbivudine treatment; ‡Data presented as the mean±standard deviation.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HBeAg, hepatitis B e antigen; TIM, telbivudine-induced myopathy; TT, telbivudine-tolerant.

cept in the regions with extensive chronic myopathic changes (Fig. 2J). PAS staining did not demonstrate glycogen storage. The vascular structure was normal. EM demonstrated various degrees of mitochondrial proliferation with subsarcolemmal or intermyofibrillar accumulation (Fig. 2K) in all of these cases. The mitochondria varied in size and presented abnormal intraorganellar architecture, including concentric cristae and a homogenized matrix (Fig. 2L).

Risk factors associated with TIM

Comparisons of demographic and clinical factors are compared between the patients with TIM and TT controls in Table 3, excluding two patients with TIM who received combined telbivudine and adefovir treatment. There were no differences in the sex, age, or diabetes mellitus and liver cirrhosis statuses between the two groups of patients. eGFR was lower in patients with TIM (72.1±27.9 mL/min/1.73 m^2) than in TT patients (91.7±28.5 mL/min/1.73 m^2, p=0.048) although CKD grades (≥3 vs. ≤2) were not different between the two groups [odds ratio (OR)=3.25, 95% confidence interval (CI)=0.68–15.5 for grade ≥3 vs. grade ≤2, p=0.125]. The prevalence of HBeAg positivity was higher in the TIM group (50%) than in the TT group (20%, p=0.041). After adjusting for relevant covariables, eGFR (OR=0.96, 95% CI=0.93–1.00, p=0.043) and HBeAg positivity (OR=6.64, 95% CI=1.01–43.5, p=0.048 in Model 2) were independently associated with TIM occurrence (Table 4).

Table 4. Multivariate regression analysis of clinical factors associated with telbivudine-induced myopathy*

Variable	Model 1		Model 2	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (yr)†	1.01 (0.93-1.10)	0.794	1.00 (0.92-1.09)	0.929
Male sex	0.62 (0.13-3.06)	0.556	0.53 (0.11-2.69)	0.445
Diabetes mellitus	2.17 (0.30-15.7)	0.445	1.66 (0.21-12.9)	0.627
Liver cirrhosis	0.44 (0.08-2.41)	0.341	0.46 (0.08-2.75)	0.397
CKD grade ≥3†	4.82 (0.54-42.7)	0.158		
eGFR (mL/min/1.73 m^2)			0.96 (0.93-1.00)	0.043
HBeAg positive	4.99 (0.83-29.9)	0.078	6.64 (1.01-43.5)	0.048

*Excluding two patients receiving combined telbivudine and adefovir treatment; †vs. grade ≤2.
CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HBeAg, hepatitis B e antigen; OR, odds ratio.

DISCUSSION

The study focused on investigations of telbivudine-associated myotoxicity with definite clinical manifestations and laboratory abnormalities due to its clinical importance. We did not find clear relationships between telbivudine treatment dosage and the development or severity of TIM. However, the patients with TIM developed myopathic symptoms after a median telbivudine treatment duration of 1.5 years. The significant latency between the start of treatment and symptom onset necessitates the constant surveillance of myotoxicity during telbivudine treatment. Persistent telbivudine use after symptom onset was also noted in some patients due to delays in linking the causality in the first place (Table 1), suggesting that the clinician needs to be vigilant about myotoxicity as well as other extrahepatic adverse reactions when using telbivudine and other NAs to treat CHB.[26]

Our case series and previous reports[13,14,17,18,22,23] have demonstrated that TIM is characterized by mitochondrial abnormalities in muscle histopathology. In our patients, the most striking pathological finding was red intracellular inclusions on mGT staining. Combined with marked elevation of SDH activity and marked accumulation and ultrastructural alterations of mitochondria on EM, these findings suggest increased mitochondrial proliferation in the affected muscle fibers. Since NAs have a similar molecular structure to nucleos(t)ides, they may inhibit the activity of human mitochondrial polymerase-γ, the primary enzyme responsible for mitochondrial DNA (mtDNA) replication. NA-related mitochondrial toxicity was first reported in nucleos(t)ide reverse transcriptase inhibitors used in antiretroviral therapy for human immunodeficiency virus (HIV) infection[27,28] and was also observed later in polymerase inhibitors used to treat CHB (a "class effect").[26] We propose that inhibiting mtDNA replication using telbivudine may lead to impairment of mtDNA-

encoded protein synthesis and to oxidative phosphorylation dysfunction and increased reactive oxygen species (ROS) production. Since cells treat an abundance of ROS as a signal of high energy expenditure related to intense physiological activity and hence an increased energy demand and need for more mitochondria, mitochondrial transcription factors A and B2 in the nuclear respiratory factor 2 pathway/antioxidant response element signaling cascade will be activated to facilitate mitochondrial proliferation as a response,[29] which results in characteristic histopathological changes.

While TIM is not often associated with obvious inflammatory reactions in muscle histopathology in our patients, other study found some cases of minimal inflammatory infiltration via CD4+ and CD8+ T-cells combined with overexpression of class I major histocompatibility complex,[19] suggesting an alternative immune-mediated mechanism in addition to mitochondrial toxicity. However, the immune activation observed in TIM may also be linked to mitochondrial damage. There is emerging evidence that mitochondria play a crucial role in immune system regulation. mtDNA and other mitochondrial components, including ATP, succinate, cardiolipin, N-formyl peptides, and transcription factor A, may serve as damage-associated molecular signals to activate the immune system.[30] The leakage of these mitochondria-derived molecules contributes to the assembly and activation of inflammasomes,[31] which are intracellular multiprotein complexes that play a crucial role in innate immunity. Moreover, some NAs used for anti-HIV therapy also induce innate immunity stimulation by activating the NLRP3 inflammasome.[32] Further investigations are needed to elucidate whether telbivudine also affects immune system homeostasis through its mitochondrial toxicity.

We found that HBeAg positivity was an independent predictor of TIM. HBeAg is critical for a persistent infection by downregulating the innate immune response of the host and increasing T-cell tolerance to HBV.[33] In patients with CHB, HBeAg positivity often indicates higher levels of viral replication and load. In contrast, longitudinal studies of immunological changes in hosts with CHB found that levels of CD4+ and CD25+ regulatory T-cells and programmed death-1 decrease, while interleukin (IL)-12, IL-21, and Th1 cytokine (IFN-γ and IL-2) levels increase along with HBeAg seroconversion.[34-36] Among NAs, an association has been found between telbivudine and a high seroconversion rate and marked decline in the HBsAg level,[37] both of which are regarded as key markers for successful treatment. HBeAg clearance associated with telbivudine treatment may ameliorate the immune tolerance to HBV infection in CHB, which may underlie the increased susceptibility to TIM in HBeAg-positive patients.

We also found an independent association between lower baseline eGFR and TIM. A longitudinal study of muscle events associated with telbivudine found that lower baseline eGFR was a significant predictor of CK elevation in patients treated with telbivudine.[38] Based on the findings of the present study, the TIM risk tended to be higher (adjusted OR= 4.82) (Table 4) in patients with CKD grade 3 or higher (i.e., eGFR ≤60 mL/min/1.73 m^2). These data suggest that impaired baseline renal function increases the risk of telbivudine-induced myotoxicity. Because telbivudine is excreted in its unchanged active form primarily from the kidneys,[39] patients with worse renal function are more prone to telbivudine accumulation and may have greater risks of its side effects. Furthermore, the patients with TIM in the present study had received telbivudine at dosages adjusted for renal function as recommended, indicating that dosage adjustment cannot eliminate the TIM risk and so removes the need for its close monitoring in patients with impaired renal function.

This study was subject to some limitations. First, the study was limited by its retrospective nature and not assessing changes in clinical (disease course and recovery) and virological (e.g., HBeAg seroconversion) factors, and blood biochemistry (e.g., lactic acid or lactate dehydrogenase levels) in patients with TIM, or their clinical courses and long-term prognoses. Second, the study did not include data on CK levels in TT cases. It is unclear whether the risk factors for TIM identified in this study can also be applied to TT cases with telbivudine-induced asymptomatic CK elevation. Third, an association has also been found between telbivudine and peripheral neuropathy.[40] The coexistence of peripheral neuropathy and its contribution to muscle weakness in these patients with TIM was not investigated.

In conclusion, we found that mitochondrial abnormalities are the characteristic histopathological features of TIM. Mitochondrial toxicity may constitute the pathogenic mechanism for TIM by inhibiting mtDNA replication and mtDNA-encoded protein synthesis, immune activation induced by mitochondrial components released by damaged mitochondria, and immune tolerance amelioration through HBeAg seroconversion. In terms of clinical implications , constant surveillance of myotoxicity during telbivudine treatment is warranted due to the possible significant latency between the start of treatment and myopathy onset. Dose adjustment does not eliminate the risk of severe telbivudine-induced myotoxicity in patients with impaired renal function.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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