

Case Report

Clevudine myopathy in patients with chronic hepatitis B[☆]

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Clevudine (L-FMAU) is a thymidine L-nucleoside analogue that was recently introduced for the treatment of chronic hepatitis B virus infection. Previous studies showed that clevudine has potent and sustained antiviral activity without causing viral resistance. No severe adverse event occurred during clinical trials. We describe two cases of drug-induced myopathy during long-term treatment of chronic hepatitis B with clevudine.

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1. Introduction

Clevudine [L-FMAU, (1-(2-fluoro-5-methyl-β,L-arabinofuranosyl) uracil)] is a pyrimidine L-nucleoside analogue with potent and sustained antiviral activity against hepatitis B virus (HBV) [1–3]. It is an enantiomer of [D-FMAU, (1-(2-fluoro-5-methyl-β,D-arabinofuranosyl) uracil)] and is structurally related to fialuridine [D-FIAU, (1-(2-deoxy-2-fluoro-β, D-arabinofuranosyl) iodouracil)], lamivudine and telbivudine [4]. Although previous studies have demonstrated the antiviral efficacy

and safety of clevudine during and after short-term treatment, corresponding data on long-term treatment with clevudine is limited.

Antiviral nucleoside/nucleotide analogue-induced myopathies were reported for fialuridine treatment for chronic hepatitis B and zidovudine treatment for HIV [5,6]. The mechanism by which myopathy is induced by these drugs involves inhibition of mitochondrial DNA polymerase γ, which results in mitochondrial DNA dysfunction *in vitro* [7]. Recently, cases of telbivudine-induced myopathy have been reported. However, there were no severe adverse effects, including myotoxicity, in clinical clevudine trials [8–12].

We describe clinical features and pathologic findings for two patients with myopathy who received clevudine therapy for chronic hepatitis B. To our knowledge, this is the first report of clevudine-related myopathy that is not associated with mitochondrial damage.

2. Case report

Case 1. A 42-year-old female who received clevudine therapy for chronic hepatitis B presented with progressive weakness of both lower legs and had experienced difficulty in chewing over the previous four months. She had chronic hepatitis B for more than 10 years

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Abbreviations: L-FMAU, (1-(2-fluoro-5-methyl-β, L-arabinofuranosyl) uracil); HBV, hepatitis B virus; D-FMAU, (1-(2-fluoro-5-methyl-β, D-arabinofuranosyl) uracil); D-FIAU, (1-(2-deoxy-2-fluoro-β, D-arabinofuranosyl) iodouracil); ALT, alanine aminotransferase; EMG, electromyography; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

and had been taking 30 mg of clevudine once daily for 16 months. She had not taken any other medication during the clevudine therapy. After clevudine therapy, her HBV DNA level decreased to an undetectable level and her serum ALT level normalized. The patient suffered from progressive and generalized weakness, especially of the legs, and experienced difficulty in climbing stairs. However, she did not have dysphagia, cramps or sensory symptoms. She exhibited motor weakness (grade 4) of the hip flexor making her difficult to stand up from the sitting position, but there was no sign of abnormal deep tendon reflex, muscle atrophy or hypertrophy on physical examination. Laboratory analyses showed an elevated creatine kinase level (220 U/L), whereas lactic acid concentration was within the normal range (Table 1, Case 1). Tests for serum autoimmune markers (anti-nuclear antibody, anti-double-strand-DNA antibody, acetylcholine receptor antibody, and anti-Jo1 antibody) were all negative. Tests for serum tumor markers (alphafetoprotein, carcinoembryonic antigen, CA19-9, and CA-125) were all within the normal

range. Stool occult blood test was negative. Abdominal sonography and gastroduodenoscopy showed no malignant lesion. Electromyography (EMG) showed a few positive sharp waves or fibrillation potentials with early recruitment of myopathic motor unit action potentials (MUAPs) in the right deltoid, vastus medialis, gastrocnemius, lumbar paraspinal and orbicularis oris muscles, which is consistent with the active stage of generalized myopathy (Fig. 1A and B). A biopsy specimen was taken from the left vastus lateralis muscle. On light microscopic examination of the specimen, there was significant size variation of myofibers revealing many degenerating and necrotic myofibers (Fig. 2A). The necrotic myofibers showed inflammatory cellular infiltrate that was mainly composed of macrophages (Fig. 2A). There were little infiltrate of inflammatory cells in perivascular spaces and no endomysial fibrosis. The specific findings of other primary myopathies such as inclusion myopathy or mitochondrial myopathy were not observed during the electron microscopic examination. The patient took 50 mg prednisolone once daily

Table 1
Laboratory results in the two cases with clevudine myopathy.

	Patient 1			Patient 2			Normal reference range
	Before clevudine therapy (April 26, 2007)	Diagnosis of myopathy (July 29, 2008)	Last follow-up (January 12, 2009)	Before Clevudine therapy (May 29, 2007)	Diagnosis of myopathy (October 10, 2008)	Last follow-up (February 24, 2009)	
WBCs ($10^9/L$)	5760	4.53	4.83	4.64	2.03	2.92	4 ~ 10
Hemoglobin (g/dL)	13.1	12.6	14.0	13.0	12.7	12.5	11.5 ~ 14.5
Platelets ($10^9/L$)	170	162	187	105	99	86	140 ~ 400
Prothrombin time (INR)	–	1.11	1.08	1.08	1.10	1.11	0.8 ~ 1.2
Total bilirubin (g/dL)	0.6	0.4	0.7	0.5	0.7	0.6	0.2 ~ 1.2
AST (IU/L)	110	40	26	59	111	59	7 ~ 38
ALT (IU/L)	172	32	24	39	59	35	4 ~ 43
Albumin ($\mu g/dL$)	4.5	3.9	4.3	4.0	3.8	4.0	3.3 ~ 5.3
LDH (IU/L)	154	650	432	433	1403	430	263 ~ 450
Creatinine (mg/dL)	0.6	0.7	0.8	0.9	0.6	0.7	0.6 ~ 1.3
Creatine kinase (U/L)	43	220	96	69	526	68	29 ~ 145
Myoglobin (ng/mL)	–	120.6	–	–	–	–	~116.3
Aldolase (U/L)	–	8.3	–	–	33.3	–	~7.6
Calcium (mg/dL)	9.5	8.9	9.0	9.1	9.7	9.6	8.0 ~ 10.8
Phosphate (mg/dL)	4.3	3.6	4.6	4.2	4.5	4.2	2.5 ~ 5.5
Lactic acid (mmol/L)	–	–	1.7	–	–	–	0.5 ~ 2.2
HbsAg	Positive	Positive	Positive	Positive	–	–	–
Anti-HBs	Negative	Negative	–	Negative	–	–	–
HbeAg	Negative	Negative	Negative	Positive	Negative	Positive	–
Anti-HBe	Positive	Positive	Positive	Positive	Positive	Positive	–
HBV DNA (copies/mL)	3.22×10^7	<300	<300	6.23×10^5	<300	<300	300 copies/mL (detect limit)
HCV antibody	Negative	Negative	–	Negative	–	–	–
HIV antibody	–	Negative	–	Negative	–	–	–
Alphafetoprotein (ng/mL)	3.0	2.99	2.20	2.83	43.12	1.79	~7.0

Abbreviations used: AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; HbsAg, hepatitis B surface antigen; Anti-HBs, anti-hepatitis B surface antibody; HbeAg, hepatitis B e antigens; Anti-Hbe, anti-hepatitis B e antibody; HBV DNA, hepatitis B virus DNA; –, not available.

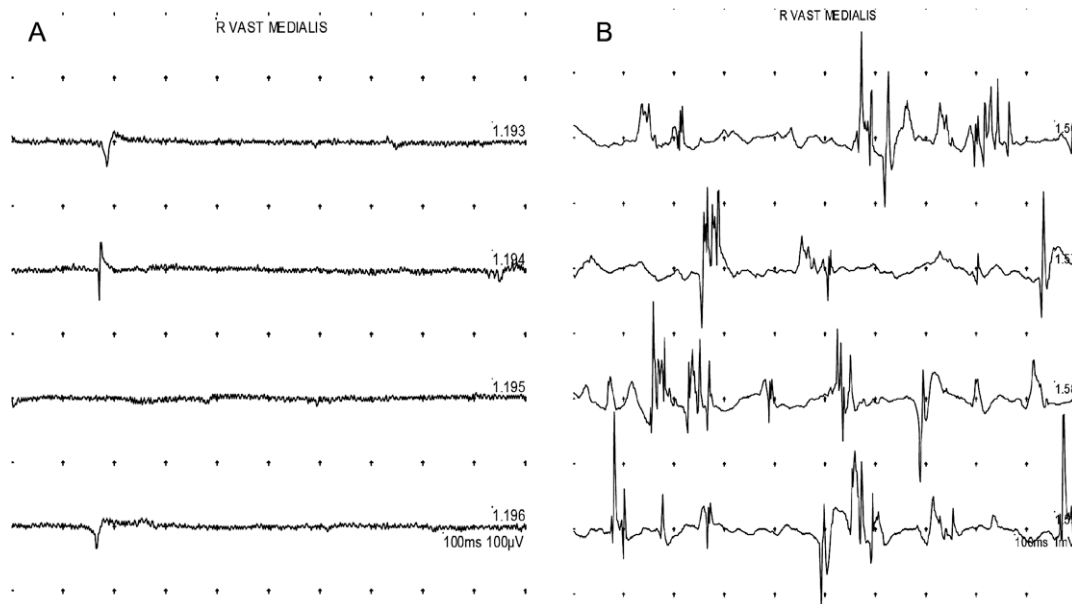


Fig. 1. Electromyographic findings in right vastus medialis muscle of Case 1. (A) Abnormal spontaneous activities and (B) low amplitude, highly polyphasic motor unit action potentials with muscle contraction were compatible with myopathic changes.

because of a diagnosis of polymyositis. Despite the steroid treatment, her serum creatine kinase level increased to 750 U/L and there was no clinical improvement in the muscle weakness. At that stage, we were unaware of the association between myopathy and long-term clevudine use. Both clevudine and prednisolone were withdrawn because of the possibility of drug-induced myopathy. Her creatine kinase level subsequently normalized to 117 U/L two months after clevudine withdrawal. Her clinical symptoms subsequently improved to the extent that she could easily climb stairs (Fig. 3A).

Case 2. A 45-year-old female with chronic hepatitis B and hepatocellular carcinoma (HCC) was admitted for combined transarterial chemoembolization (TACE) and radiofrequency ablation treatment for recurrent HCC. She had undergone hepatic segmentectomy for HCC seven years previously and had undergone TACE 15 months previously. She had taken 30 mg of clevudine once daily for 13 months for treatment of chronic hepatitis B with high viraemia (6.23×10^5 copies/mL, Cobas Amplicor HBV Monitor, Roche). Her serum HBV DNA level decreased to an undetectable level and

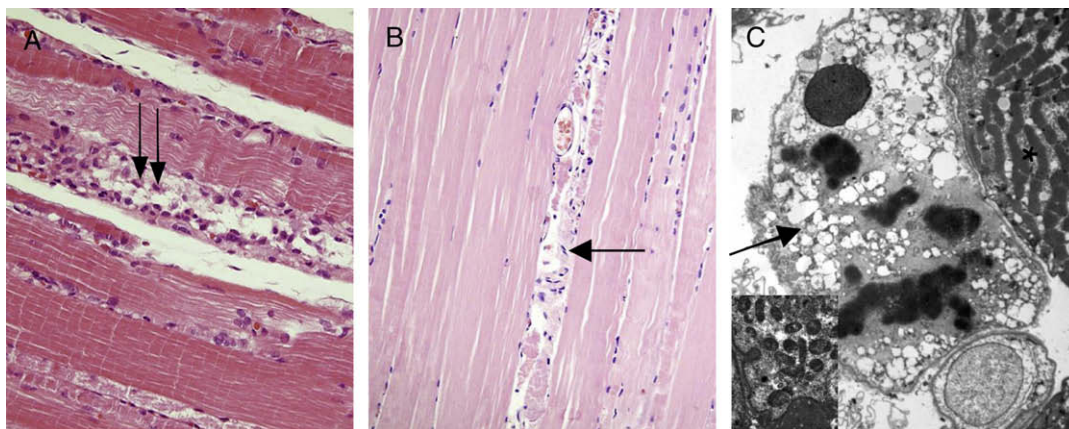


Fig. 2. Muscle biopsy specimens. (A) The muscle biopsy specimen from Case 1 revealed many degenerating and necrotic myofibers with macrophage infiltration. Black arrows indicate macrophage infiltrate in the necrotic myofibers (haematoxylin–eosin-stained paraffin section; original magnification, 200 \times). (B) The muscle biopsy from Case 2 shows a severely necrotic myofiber indicated by black arrow compared with the adjacent intact other myofibers (haematoxylin–eosin-stained paraffin section; original magnification, 200 \times). (C) Electron micrograph of a muscle biopsy from Case 2 showed a necrotic myofiber (arrow) with severe degeneration of subcellular organelles compared with the adjacent intact myofiber (*). No mitochondrial alteration suggestive of mitochondrial myopathy is identified (inset, left lower).

HBeAg loss was observed after the clevudine therapy. However, she experienced weakness of both legs for two months. She could not climb stairs and struggled to get to her feet. She did not take any other medication or undergo chemotherapy during the clevudine therapy. On neurological examination, she showed Gowers' maneuver using her hands and arms to stand up her body from a squatting position. Muscle strength of both distal legs was normal. Her serum creatine kinase level on admission (526 U/L) was markedly elevated compared with baseline (69 U/L) and peaked at 1259 U/L

(Table 1, Case 2). Tests for serum autoimmune markers (anti-nuclear antibody, anti-double-strand-DNA antibody, acetylcholine receptor antibody, and anti-Jo1 antibody) showed all negative. Serum alphafetoprotein increased to 42.12 ng/ml, however, serum carcinoembryonic antigen, CA19-9, and CA-125 were within the normal range. The Papanicolaou smear screening test for cervical cancer showed no malignant cell. Computed tomographic scans of abdomen and pelvis only showed an 8 mm sized marginal recurrence of hepatocellular carcinoma. No malignant lesion was present on the

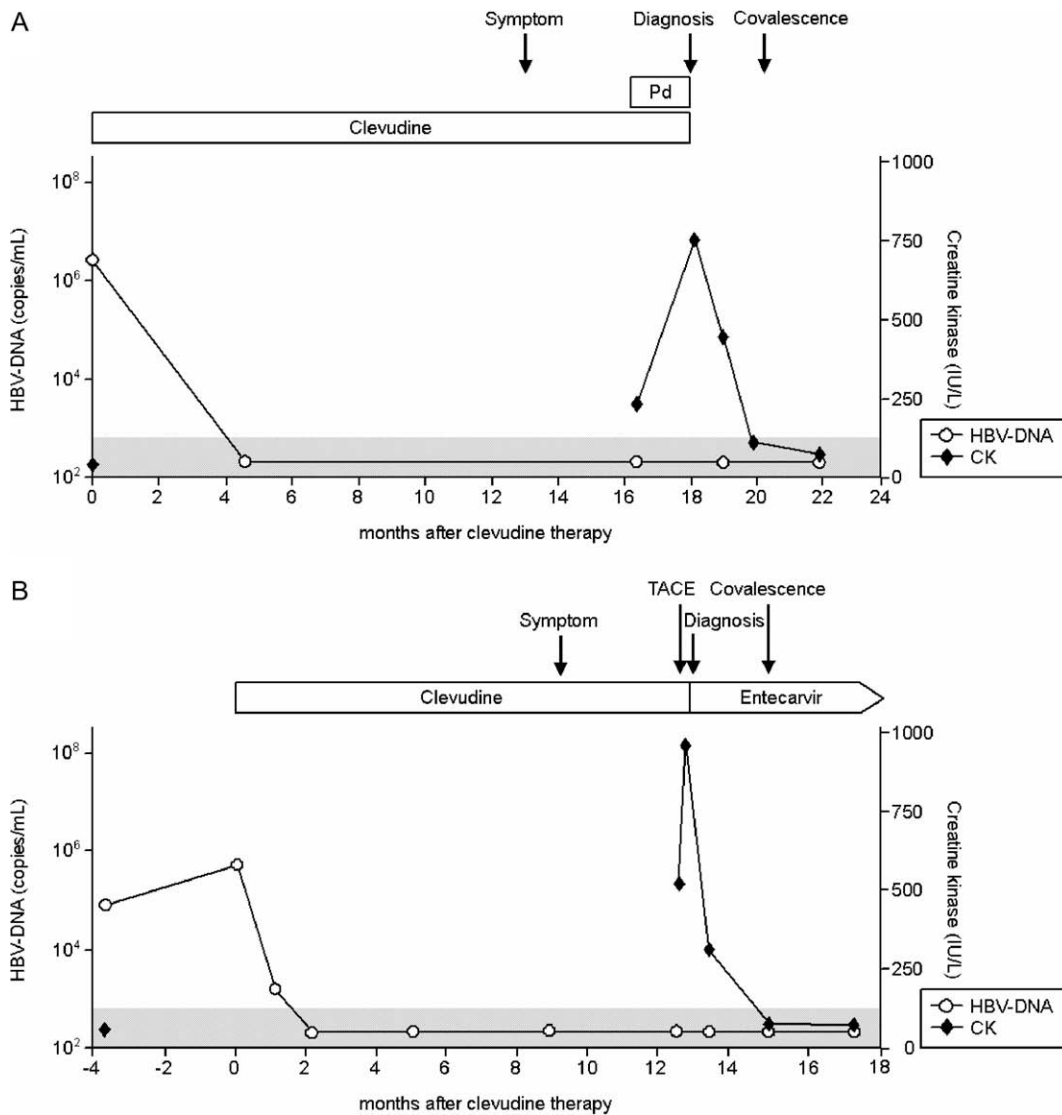


Fig. 3. Changes in serum creatine kinase level and HBV DNA for two patients who were treated with clevudine. (A) Case 1 exhibited myopathic symptoms 12 months after starting clevudine treatment and was diagnosed with myopathy 16 months after beginning treatment. Steroid was then administered for the myopathy. Clevudine and prednisolone treatment were discontinued 18 months after commencement of clevudine treatment because there was no clinical improvement in muscular symptoms. Two months later, she reported an improvement in the muscle weakness, and the levels of serum creatine kinase were normal. (B) Case 2 experienced muscle weakness nine months after clevudine treatment. She did not report the general weakness to doctor until she was admitted to the hospital for treatment of recurrent HCC. Drug-induced myopathy was diagnosed after 13 months of medication and clevudine was replaced with entecarvir. One month later, she reported an improvement in muscle power, and her creatine kinase level decreased. CLV, clevudine; ETV, entecarvir; Pd, prednisolone; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

gastroduodenoscopy. Myopathic changes were noted on EMG. A muscle biopsy was performed on the vastus lateralis muscle and it showed many regenerating and degenerating atrophic myofibers including many necrotic myofibers infiltrated by macrophages under light microscopic examination (Fig. 2B). The necrotic myofibers revealed degenerated cytoplasmic organelles and no significant alteration of mitochondria is noted under the electron microscopic examination (Fig. 2C). Selective type 2 fibre atrophy was evident after staining for myosine ATPase and nicotinamide adenine dinucleotide-tetrazolium reductase. The pathologic features indicative of neurogenic, myogenic or metabolic aetiologies, including mitochondrial myopathy were not observed in the muscle biopsy specimen. Clevudine was switched to entecavir (0.5 mg/d). The muscle weakness disappeared one month after clevudine withdrawal and the creatine kinase level decreased to 68 U/L at five months after clevudine withdrawal (Fig. 3B).

3. Discussion

Clevudine is a nucleoside analogue of the unnatural L-configuration and has potent anti-HBV activity *in vitro* and *in vivo* and a favourable toxicity profile in all species tested [1–3]. In phase II clinical studies, clevudine exhibited potent antiviral activity, was well tolerated and had no dose-limiting toxicity [8]. The lack of cytotoxicity reflects the inability of human cellular DNA polymerases α , β , γ and δ to utilize the 5'-triphosphate moiety of clevudine as a substrate. Moreover, clevudine was found to have no effect on mitochondrial structure, DNA content, or function in animal and *in vitro* studies [2,13]. None of the many clinical clevudine trials reported severe adverse effects, including myotoxicity [8–12]. Clevudine is a unique antiviral nucleotide analogue because its antiviral activity persists after discontinuation of therapy, as demonstrated by *in vitro* and *in vivo* trials [3,9–11]. Therefore, it is a promising treatment option for chronic HBV infection [14]. To date, the results of five clinical trials on clevudine therapy have been published, including phase II studies that showed that there were no serious adverse events after treatment for 24 weeks [8–12]. Although it was approved for the treatment of chronic HBV infection in South Korea in November 2006, long-term data on its safety and antiviral efficacy are limited.

We observed two cases of myopathy during clevudine therapy for chronic hepatitis B. The clinical symptoms of myopathy developed after 12 and 10 months of clevudine treatment, respectively. A diagnosis of clevudine-induced myopathy was made 18 and 13 months after commencing clevudine treatment, respectively. Levels of serum creatine kinase and lactate dehydrogenase were elevated, but lactic acidosis did not occur. The EMG findings

were consistent with those of chronic myopathy and there was no evidence of nerve damage. Muscle biopsies revealed necrosis of myofibers and inflammatory cell infiltration, but the electron-microscopic examination did not show evidence of mitochondrial damage. The muscle biopsy features are similar to those of steroid-induced myopathy in toxic myopathies [15,16]. The clinical and laboratory findings showed no evidence of myasthenia gravis, polymyositis associated with autoimmune diseases, dermatomyositis, inclusion body myositis or muscle weakness by paraneoplastic syndrome. The muscle-related symptoms in the cases resolved after cessation of clevudine treatment. Taken together, the muscle damage was diagnosed as clevudine-induced myopathy.

Nucleoside/nucleotide analogue-induced myopathy occurs during treatment with fialuridine for chronic hepatitis B and treatment with zidovudine for HIV [5,6]. These drugs induce mitochondrial DNA dysfunction by inhibiting mitochondrial DNA polymerase γ [7]. Even though fialuridine treatment caused no serious adverse events in animal and preliminary studies, it has been reported that most chronic hepatitis B patients who are treated with fialuridine develop severe myopathy, lactic acidosis and eventually die [5]. Recently, the phase III GLOBE study reported three symptomatic myopathic cases out of 680 patients who received telbivudine. This study also showed that an adverse event, a grade 3 or 4 elevation in serum creatine kinase level, occurred in 9% of patients receiving telbivudine [17]. A Chinese study showed that five of 105 chronic hepatitis B patients who received telbivudine treatment developed clinical myopathy [18].

There were no *in vitro* and *in vivo* studies that demonstrated the possible mechanism of clevudine-associated myopathy. The mechanisms of zidovudine-induced myopathy have alluded that apoptosis of skeletal muscle cells can be caused by direct mitochondrial DNA depletion, mitochondrial dysfunction and oxidative stress, and a depletion of L-carnitine [6]. It has been suggested that zidovudine causes damage to mitochondria by impairment of respiratory chain and mitochondrial protein synthesis [19]. Because our cases showed no evidence of mitochondrial damage on electron microscopic finding, the mechanism of clevudine-induced muscle damage might be oxidative stress, a depletion of any substrate, or disturbance of protein synthesis, like alcohol or steroid-induced myopathies. Further *in vitro* and *in vivo* studies are needed to demonstrate the mechanism of clevudine-induced myopathy.

Considering the structural similarity between clevudine and telbivudine, myopathy that develops during clevudine therapy may be regarded as clevudine-induced and as a serious adverse event. There was a time lag of six months between the onset of myopathic symptoms and the cessation of clevudine treatment for Case 1. Because of an inappropriate diagnosis of polymyositis,

this patient was treated with a steroid in addition to clevudine for a further two months. Case 2 had taken clevudine for 13 months. She did not mention her general weakness to the doctor until she was admitted to the hospital for treatment of recurrent HCC. Although proper management was delayed in our cases, cessation of clevudine treatment resulted in amelioration of myopathic symptoms and normalization of creatine kinase levels.

In conclusion, during long-term clevudine treatment, particular attention should be paid to muscular symptoms, and muscle enzyme levels should be monitored. Any symptoms or signs associated with muscle damage should be evaluated promptly. We report two cases of drug-induced myopathy during clevudine therapy for chronic hepatitis B. Further investigations are needed to clarify the safety and efficacy of long-term clevudine therapy.

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