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Lamivudine Therapy Exacerbates Bilirubinemia in Patients Underlying Severely Advanced Hepatitis

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Lamivudine belongs to the set of antiviral agents effective against hepatitis B virus infection. Given case reports on liver injuries after certain antiviral agent treatments, this study examined the effects of lamivudine on alanine aminotransferase (ALT) and total bilirubin (TB) using a medical system database. A total of 1,321 patients taking lamivudine alone or with others were evaluated using laboratory hits in an electronic medical system at Seoul National University Hospital from 2005 through 2011. The patients were grouped according to prior ALT results: G#1, ALT < 40 IU/L; G#2, 40 IU/L ≤ ALT < 120 IU/L; G#3, 120 IU/L ≤ ALT < 240 IU/L; and G#4, ALT ≥ 240 IU/L. In G#1 and G#2 patients, lamivudine or adefovir treatment decreased ALT and TB compared to prior values. In G#3 and G#4 patients with three times the upper limit of normal (ULN) ≤ ALT < 15 times the ULN, both ALT and TB were decreased after treatment with lamivudine alone, or adefovir following lamivudine therapy, indicating that lamivudine therapy ameliorated liver functions. However, in G#4 patients who experienced severely advanced hepatitis (ALT ≥ 15 times the ULN, or ≥ 600 IU/L), lamivudine augmented TBmax (6.3 → 13.3 mg/dL) despite a slight improvement in ALT (839 → 783 IU/L), indicative of exacerbation of bilirubinemia. Patients who used adefovir after lamivudine also showed a high incidence of hyperbilirubinemia when they experienced severely advanced hepatitis. Treatment with adefovir alone did not show the effect. In conclusion, lamivudine may increase the risk of hyperbilirubinemia in patients with severely advanced hepatitis, implying that caution should be exercised when using lamivudine therapy in certain patient populations.

***Key words*:** Lamivudine, Drug-associated hyperbilirubinemia, Laboratory signal hits, Total bilirubin, ALT

INTRODUCTION

Chronic hepatitis B virus (HBV)-infected patients are characterized by high alanine aminotransferase (ALT) activities, possibly accompanying jaundice and hepatic decompensation (1). Lamivudine, a cytosine nucleoside analogue, inhibits viral replication by acting on HBV DNA polymerase and inducing chain termination. Lamivudine improves the parameters of liver function and histopathology, such as fibrosis, HBeAg seroconversion, or ALT normalization (2-7). Generally, lamivudine therapy allows HBV-infected patients to recover ALT and/or aspartate transaminase (AST) activities to normal ranges through virus eradication and is often recommended for long-term treatment rather than limited

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Abbreviations: ADR, adverse drug reaction; ALT, alanine aminotransferase; AST, aspartate transaminase; EMR, electronic medical record; TB, total bilirubin (TB); UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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course treatment (8). It is also administered with other drugs, such as adefovir and entecavir, to enhance antiviral efficacy.

It should be noted, however, that some anti-viral agents, particularly those requiring a high-dosage treatment regimen, have the potential to initiate chemical-induced liver injury. Due to the burden of metabolic detoxification, especially for those with underlying severely diminished liver function, caution should be exercised when using antiviral therapy. In fact, the possibility of adverse drug reaction (ADR) occurrences induced by lamivudine and/or other anti-viral agents has been proposed in some case studies, e.g., lamivudine treatment acutely exacerbated hepatocyte injury in those with chronic hepatitis (8). Therefore, lamivudine-induced liver injury particularly in patients suffering from advanced liver diseases is possible. Moreover, large-scale database analyses for this possibility have not been carried out. Thus, an understanding of the ADRs of anti-viral agents in the context of liver dysfunction may be of assistance to accomplish successful long-term therapy.

To create a data-acquisition method using electronic medical records (EMRs) and apply the result for the assessment of ADR types and incidences, factors such as patient laboratory signals, genders, ages, organ functions, pathological factors, and co-administered drugs should be analyzed (9). In addition, drug-associated factors may be deduced from incidence rates, severity, duration time, and onset time of the parameters of interest. For liver function, cholestasis, and other liver-related disease conditions, parameters including total bilirubin (TB) and ALT and AST activities in blood may provide clues (10,11). In general, ALT and AST activity indicate the severity of hepatitis, whereas blood bilirubin content reflects the extent of not only hepatocyte injury, but detoxifying capacity. Hence, blood bilirubin content generally reflects liver function as bilirubin is produced when the liver removes heme derived from old red blood cells. In most cases, hyperbilirubinemia causes jaundice, which may be further exacerbated by pathologic hepatic conditions and hepatitis.

It has been claimed that anti-viral treatment regimens containing a fixed-dose combination of paritaprevir, ritonavir, and ombitasvir may cause serious liver injury in patients with underlying advanced liver disease (12), suggesting that certain antiviral medications impose metabolic burdens to patients presumably due to the drug intermediates produced. Also, relatively larger doses of lamivudine are given compared to other anti-viral agents, with common oral doses of lamivudine, adefovir, and entecavir being 300, 10, and 0.5 mg/day, respectively (13-15). Given these points, this study assessed the effects of lamivudine treatment alone or in conjunction with adefovir using parameters representing liver function in groups of patients with mild, moderate, or severe hepatitis. We found that lamivudine alone or adefovir after lamivudine therapy may enhance the risk of hyperbilirubinemia in patients with severely advanced hepatitis.

MATERIALS AND METHODS

Study population. This study was approved by the Institutional Review Board of Seoul National University Hospital (SNUH, IRB No. 1012-046-344), which is a 1,961-bed medical center in Korea. The database contained records of 496,530 patients (≥ 18 years), who had been admitted to SNUH and had undergone liver function tests from January 2005 through December 2011. The retrieved data had anonymous codes representing patient files comprising age, gender, medical diagnosis codes, blood ALT and AST activities, TB contents, dates of laboratory samples drawn, and medications (including generic or brand name, prescription date, and duration).

Patients. Patients were 18 years or older, were prescribed with lamivudine, adefovir, and/or entecavir, and had at least three data points of ALT, AST, albumin, and TB measurements during anti-viral therapy documented in their medical records. As a result, laboratory data were obtained from 353 patients using the EMR system. They were divided into four groups according to prior ALT ranges; G#1, ALT < 40 IU/L; G#2, 40 IU/L ≤ ALT < 120 IU/L; G#3, 120 IU/L ≤ ALT < 240 IU/L; and G#4, ALT ≥ 240 IU/L. In each group, other parameters were also retrieved to monitor changes in liver function prior to or during lamivudine treatment. Maximum total bilirubin (TBmax) content was used to assess drug effects on liver function because the content represents the functional remaining liver fraction (i.e., the detoxifying capacity).

Data acquisition and the mining process. TB measurements were sorted into categories according to the preexisting history of use of lamivudine, adefovir, entecavir, and other concomitant drug treatments. The steps for extraction and the data mining process are presented in Supplementary Fig. 1. Inclusion or exclusion criteria for each laboratory signal (i.e., ALT and TB in the blood) were critical for optimal patient grouping. First, patients having one or two data points for either ALT and TB were excluded. Second, TB contents determined prior to the first measurement were assumed to be in a normal range of < 1.4 mg/dL. Similarly, ALT and AST activities were considered within a normal range when < 40 mg/dL. They were used as cut-offs for bilirubinemia or abnormal liver function. Third, the incidence rate of hyperbilirubinemia was expressed as a percentage in each group. Data is shown as the median (minimum-maximum) in Tables 1 and 2. To assess the potential of drug-induced hyperbilirubinemia, patients who used adefovir after lamivudine therapy were additionally analyzed.

Data analysis. Microsoft Excel and Access software and Microsoft Excel functions (version 2013) were used to analyze ALT, TB, and the other parameters. The results were considered statistically significant if the *p*-value was less than 0.05. Statistical analyses were conducted using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Analysis of patients subjected to lamivudine therapy. The baseline characteristics of patients is summarized in Table 1. In those who had no hepatitis (G#1), either serum ALT activities or TB contents were not significantly different during the period of lamivudine therapy as compared to the baselines. In G#1, lamivudine treatment had no effect on our parameters of interest. In G#2, lamivudine decreased ALT by 35%; TBmax values were reduced to a greater degree (72%; 2.5 to 0.9 mg/dL) (Fig. 1A). In G#3, ALT activity and TBmax were decreased 24.7% and 45.9%, respectively. Thus, lamivudine therapy lowered TBmax to a larger extent than ALT in patients who had a moderate degree of hepatitis. In G#2 and G#3, ALT and TB were widely scattered after lamivudine treatment compared to the baselines observed prior to therapy. In G#4, lamivudine treatment ameliorated TBmax less than ALT (3.7% versus 9.8%) (Fig. 1B). Intriguingly, administration of lamivudine to a subgroup of patients who had experienced severely advanced hepatitis (i.e., ALT ≥ 15 times ULN; ALT ≥ 600 IU/L) greatly increased TBmax (from 6.3 to 13.3 mg/dL), although ALT was slightly improved (from 839 to 783 IU/L).

Next, we performed sub-group analyses for patients in G#3 and G#4 using a TBmax cut-off of 4.2 mg/dL (i.e., three times ULN). ALT and TB, and the differences between prior to use and during use of lamivudine medication, are summarized in Table 2. ALT_0 and ALTmax were 77.9% and 81.4% greater, respectively, in patients with high TBmax (i.e., ≥ 4.2 mg/dL) than those with low TBmax (i.e., < 4.2 mg/dL). In high TBmax patients, neither ALT nor TB were improved. By contrast, low TBmax patients showed an improvement in TB, but not in ALT, suggesting that TB content may represent functional liver fraction more sensitively.

Another correlation analysis was done on ALT differences and TBmax. Patients showing abnormal TBmax were 19.3% (n = 32 patients having abnormal TBmax versus a total of 166 patients), 13.3% (11 versus 83), 31.1% (14 versus 45) and 79.7% (47 versus 59) in G#1, G#2, G#3, and G#4, respectively. The data showing abnormal TBmax were re-analyzed for ALT differences and TBmax. Among the patients with abnormal TBmax in G#1 and G#2, there was a positive correlation between ALT increases and TBmax

Table 1. ALT activities and TB contents before and during antiviral therapy

	G1	G2	G3	G4
Lamivudine	n = 166	n = 83	n = 45	n = 59
Age (years)	53 (21~63)	48 (24~61)	59 (21~58)	55 (25~69)
Gender (M, F)	89, 77	47, 36	30, 15	32, 27
ALT (IU/L)				
Before	25 (12~38)	89 (42~118)	192 (121~216)	592 (253~1348)
During	38 (8.1~43)	63 (21~125)	183 (64~954)	455 (91~1065)
TB (mg/dL)				
Before	1.8 (0.2~3.2)	2.5 (1.2~4.3)	6.1 (4.3~7.6)	8.1 (4.8~9.6)
During	0.8 (0.3~3.5)	0.9 (0.8~4.3)	3.3 (0.4~18.3)	6.8 (0.8~11.3)
Adefovir	n = 103	n = 63	n = 41	n = 42
Age (years)	51 (23~65)	47 (22~65)	53 (20~59)	51 (22~71)
Gender (M, F)	51, 52	31, 32	15, 26	12, 30
ALT (IU/L)				
Before	21 (11~36)	72 (43~102)	171 (121~222)	512 (242~912)
During	29 (10~43)	63 (32~115)	152 (95~624)	355 (98~998)
TB (mg/dL)				
Before	1.8 (0.2~3.2)	2.2 (1.2~4.3)	5.1 (4.3~7.6)	7.1 (4.8~8.6)
During	1.6 (0.3~3.8)	1.3 (0.8~3.9)	4.5 (0.6~8.2)	7.5 (1.2~10.3)
Entacavir	n = 85	n = 63	n = 32	n = 38
Age (years)	50 (22~60)	49 (26~58)	52 (23~68)	48 (21~63)
Gender (M, F)	39, 46	37, 26	11, 21	20, 18
ALT (IU/L)				
Before	17 (11~38)	71 (41~117)	155 (121~201)	465 (242~819)
During	30 (13~43)	63 (26~110)	147 (69~305)	316 (153~965)
TB (mg/dL)				
Before	1.4 (0.2~2.3)	2.2 (1.3~4.4)	5.1 (2.3~7.6)	5.6 (2.6~8.6)
During	1.3 (0.3~3.8)	1.3 (0.6~4.3)	3.5 (0.6~8.2)	3.9 (1.1~10.3)

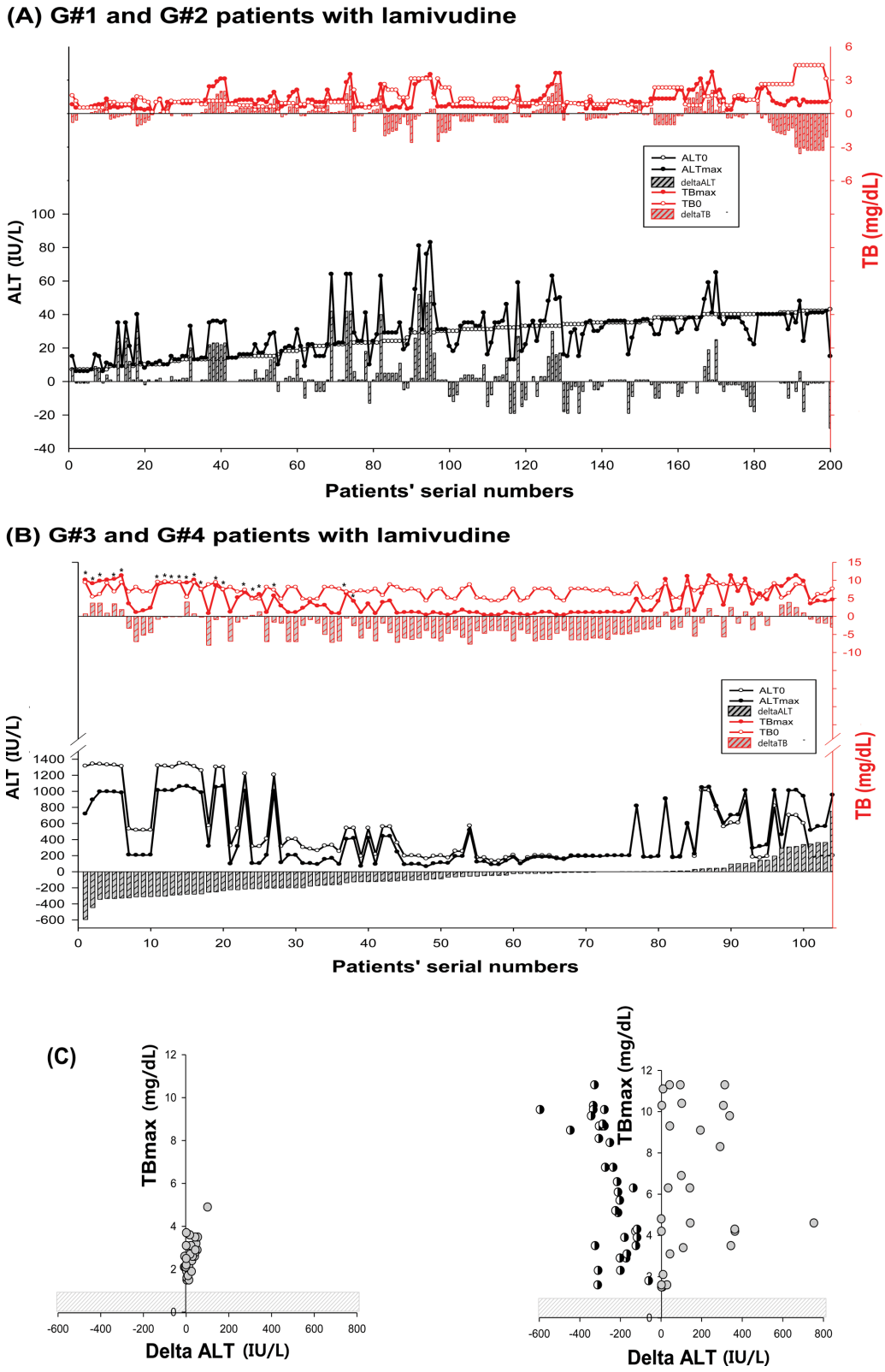

Fig. 1. (A, B) ALT_0, ALT_{max}, TB_0, and TB_{max} values before and during lamivudine therapy in G#1 and G#2 groups or in G#3 and G#4 groups. The differences between prior to and during therapy are shown as delta ALT (IU/L) or delta TB (mg/dL). (C) The relationship between delta ALT (IU/L) and TB_{max} (mg/dL) in patients showing $TB_{max} > 1.4$ mg/dL in G#1 and G#2 groups (left) or in G#3 and G#4 groups (right; ●, patient with an increase of ALT; and ◐, patient with a decrease of ALT). ◑ is indicated as * in panel (B).

Table 2. ALT activities and TB contents before and during antiviral therapy in G#3 and G#4

	3 × ULN ≤ ALT < 15 × ULN		ALT ≥ 15 × ULN	
	Delta ALT (–)	Delta ALT (+)	Delta ALT (–)	Delta ALT (+)
Lamivudine (n = 103)				
Delta TB (–)	62*	3	2	1
Delta TB (+)	6*	12	13*	4
Adefovir (n = 83)				
Delta TB (–)	39*	10	4	0
Delta TB (+)	8	11	10*	1
Adefovir alone (n = 53)				
Delta TB (–)	27*	6	3	0
Delta TB (+)	4	9	3	1
Lamivudine + Adefovir (n = 30)				
Delta TB (–)	12*	4	1	0
Delta TB (+)	4	2	7*	0
Entacavir (n = 70)				
Delta TB (–)	41	2	11	3
Delta TB (+)	3	5	2	3

*$p < 0.01$, significantly different between delta ALT (–) and delta ALT (+) in each antiviral therapy using Fisher's exact test.

(Fig. 1C, left). In G#3 and G#4, patients with abnormal TBmax showed two populations: abnormal TBmax and ALT amelioration versus abnormal TBmax and ALT exacerbation (Fig. 1C, right).

ALTmax and TBmax were compared in those who underwent adefovir and lamivudine therapy. In 83 adefovir-treated patients showing ALT greater than three times the ULN, 53 patients were prescribed with adefovir alone (67.9%), whereas 30 patients were treated with adefovir following lamivudine (36.1%). Of the patients with ALT more than three times the ULN but less than 15 times the ULN, TBmax (+) ALT (–) patients were 7 and 11, respectively, in the adefovir alone and adefovir after lamivudine therapy (4/46, 9% vs. 4/22, 18%), suggesting that adefovir after lamivudine treatment causes hyperbilirubinemia. Similar changes were observed in those showing ALT greater than 15 times the ULN (3/7, 43% versus 7/8, 88%) (Table 2). Overall, our results support the idea that lamivudine treatment may aggravate hyperbilirubinemia in a population undergoing severely advanced hepatitis.

Analysis of co-medications. To find any confounding factors potentially associated with lamivudine-induced bilirubinemia, the effects of concurrent medications, particularly those frequently prescribed with lamivudine, on ALTmax or TBmax were analyzed. Briefly, drugs co-prescribed with lamivudine were considered if prescribed within one month prior to measurement of ALTmax or TBmax. The average number of co-mediations was 4.3 drugs per day (drugs used at a frequency of 1% or less were excluded). In this analysis, silymarin, ursodeoxycholic acid (UDCA), Bease, entecavir, adefovir, prednisone, corticosteroid, tacrolimus, interferon, and/or zidovudine were often used with lamivudine, consistent with a case report (16). It has been reported that entecavir, adefovir, tacrolimus, interferon, and zidovudine treatments resulted in 110% increased risk of hepatotoxicity despite their low prescription frequencies (i.e., < 10%). In G#3 and G#4, the proportion of co-medication of lamivudine with either silymarin or UDCA was 46%. Their TBmax values were in an abnormal range, although ALT was improved. In G#4, lamivudine plus UDCA treatment showed higher ALT and TBmax than did lamivudine treatment alone.

DISCUSSION

Adverse drug reactions have become an important clinical issue and a concern in the public health system, being responsible for 6.5% of all hospital admissions, with approximately one-fourth of these patients at risk for death (17,18). The occurrence of ADRs has increased every year (4). As an effort to minimize ADRs, it is necessary to understand the causal relationship between medications and ADR incidence (2). Data acquisition from laboratory signals using patient EMRs may be of value to find ADRs and other conditions in patients (4). Three major methods are often used for ADR reports and include 1) spontaneous reports by clinicians or patients, 2) retrospective manual chart reviews, and 3) reviews of ADRs based on patient EMRs (5). Among them, reviews of EMR databases may be useful to assess the incidence of ADRs and to create an electronic alert system (7). A total of 4,690 reports of suspected drug-induced liver injury associated with fatal outcomes was found using an EMR database in a hospital setting (19).

Lamivudine was the first registered antiviral drug and is widely used due to its efficacy during short-term administration (1). It is used as a mainstream therapy for HBV patients due to its effectiveness against HBV DNA and his-

tological improvements. During anti-viral therapy, ALT is used as a biomarker to assess drug efficacy and is monitored as a general recovery factor. Despite its effectiveness, a few case reports have raised the possibility that lamivudine causes liver toxicity in certain populations (20,21). In the current study, we report that patients with underlying severely advanced hepatitis suffered from hyperbilirubinemia despite ALT amelioration, presumably due to a limited capacity for bilirubin metabolism. Nonetheless, lamivudine medication did not exacerbate bilirubinemia in patients with no, mild, or moderate hepatitis. Our results here support the possibility that lamivudine undergoes biotransformation in the liver for clearance, particularly in those having severely advanced hepatitis. This idea is strengthened by the finding that lamivudine, which requires a larger dosing amount than other antiviral agents, may have the potential to cause drug-induced liver injury (22). In this study, we paid attention to patients suffering from severely advanced hepatitis and diminished liver function, considering this possibility.

In many cases, abnormal increases of TB may result from overproduction of indirect bilirubin, inhibition of bilirubin uptake into hepatocytes, inhibition of bilirubin conjugation, and/or decreased excretion of direct bilirubin (23-26). In general, an abnormality is usually judged by TB content in the blood. In the present study, our findings raised the notion that lamivudine imposes a detoxifying burden (i.e., it inhibits bilirubin conjugation) to those with severe hepatitis, as indicated by exacerbation of hyperbilirubinemia despite ALT amelioration. This may be due to saturation of bilirubin biotransformation due to a decrease of hepatocytes and/or their dysfunction.

Our finding that lamivudine treatment had a deleterious effect and should be limited in its use for those with severe hepatitis is strengthened by our data showing improvements in both ALT and TB in populations having mild or moderate degrees of hepatitis. Unfortunately, the improvement in liver function when using lamivudine in patients with severe hepatitis was only 30% (3 out of 10 patients with chronic hepatitis B; 1). This limitation may have been associated with deterioration of hepatocyte viability, possibly due to lamivudine-induced liver injury.

Antiviral agents including lamivudine and other drugs have nucleoside moieties (14), which may require oxidation and conjugation for detoxification. Studies using animals and cells showed that lamivudine metabolism depends on CYP2B6 and CYP3A and uridine diphosphate alpha-D-glucuronic acid conjugation (27), suggesting that competition between lamivudine (metabolite) and bilirubin for glucuronide conjugation in hepatocytes. In general, lamivudine biotransformation in the liver is a minor route of elimination in healthy individuals because unchanged parent drug molecules are cleared predominately by the kidney (8). However, patients with severely advanced hepatitis may have reduced functional liver function (28). Hence, hepatic metabolism of lamivudine may influence its glucuronidation in patients having limited and decreased liver function (5~10%), presumably in conjunction with low plasma protein binding (due to low plasma albumin) (8). This may result from the first-order rate of uridine 5′-diphospho-glucuronosyltransferase conjugation (12). This contention matches with the finding that patients with severely advanced hepatitis have 35~48% viable hepatocyte mass (12). Moreover, hyperbilirubinemic severity and related jaundice may be assessed based on ALT and bilirubin levels in the blood. Excess degradation of heme and/or reduction of bilirubin excretion can also induce hyperbilirubinemia. Thus, hyperbilirubinemia may result from hemolysis, such as hemolytic anemia that increases bilirubin production, and/or from hepatic dysfunctions, such as abnormal liver function and impaired bilirubin metabolism and excretion (29). Thus, lamivudine may compete with bilirubin for organic anion transporter-mediated uptake into hepatocytes (13,16), suggesting the possibility that a high concentration of lamivudine in the blood aggravates hyperbilirubinemia. Collectively, lamivudine-induced TB elevation in patients underlying severely advanced hepatitis may reflect metabolic burden, implying that caution should be exercised for lamivudine therapy in patients experiencing severely advanced hepatitis (i.e., ALT > 600 IU/L). From our results, lamivudine-induced hyperbilirubinemia appeared to be irreversible in patients experiencing severely advanced hepatitis.

Of course, this conclusion has several limitations. Excluded factors, such as comorbidity, polypharmacy, gender, and age can affect the occurrence and severity of lamivudine-induced hyperbilirubinemia. In addition, patient information was collected from only one hospital and one specific period. These exclusions were indispensable to deduce the conclusions based on the EMR database used but it still remains a limitation of this conclusion.

In our study, adefovir and entecavir had no significant effect on TB (Table 2), presumably because they are mainly eliminated via the kidney (16,28,30). Even in patients with advanced severe hepatitis, their metabolic burden for elimination seemed to be not great. Because of the resistance of lamivudine-only therapy and the cost-effectiveness of antiviral agents, combination therapy using lamivudine and adefovir is often recommended (30-34). In the present study, patients subjected to adefovir therapy after lamivudine indeed exhibited higher TB than those with adefovir alone (Table 2), supporting the identified lamivudine effect on hyperbilirubinemia. Overall, our results support the contention that a portion of patients experiencing severely advanced hepatitis need to be carefully monitored to prevent lamivudine-induced hyperbilirubinemia.

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CONFLICT OF INTEREST

None to declare.

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