การใช้ยาลามิวูดีนเริ่มต้นในการรักษาโรคไวรัสตับอักเสบเรื้อรังชนิดบี ในโรงพยาบาลมหาวิทยาลัย: การศึกษาทบทวนประวัติผู้ป่วยย้อนหลัง

Lamivudine as Initial Treatment for Chronic Hepatitis B Virus in a University Teaching Hospital: a Retrospective Patient Record Review Study

นิพนธ์ต้นฉบับ **Original Article**

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บทคัดย่อ

วัตถุประสงค์: เพื่อประเมินผลลัพธ์ทางคลินิก เหตุการณ์ไม่พึงประสงค์และศึกษารูปแบบการเพิ่มหรือเปลี่ยนยาภายหลังการใช้ยาลามิวูดีนเป็นตัวแรกในการรักษาโรคไวรัสตับอักเสบเรื้อรังชนิดบี **วิธีการศึกษา:** เป็นการศึกษาเชิงพรรณนาแบบเก็บข้อมูลย้อนหลังในผู้ป่วยโรคไวรัสตับอักเสบเรื้อรังชนิดบีที่เริ่มต้นการรักษาด้วยยาลามิวูดีน ขนาด 150 มิลลิกรัม ณ โรงพยาบาลมหาราชนครเชียงใหม่ จ.เชียงใหม่ จำนวน 98 คน ที่เข้ารับการรักษาในช่วงวันที่ 1 มกราคม พ.ศ.2548 - 31 ธันวาคม พ.ศ. 2552 **ผลการศึกษา:** ผู้ป่วยจำนวน 98 คน แบ่งเป็นผู้ป่วยกลุ่ม HBeAg positive 55 คน (ร้อยละ 56.1) และ HBeAg negative 43 คน (ร้อยละ 43.9) โดยผู้ป่วยกลุ่ม HBeAg positive พบการเกิด seroconversion ร้อยละ 16.4 และมีระดับ HBV DNA ต่ำจนตรวจไม่พบต่ำกว่ากลุ่ม HBeAg negative (ร้อยละ 18.2 และ ร้อยละ 53.5) แต่พบว่ามีระดับของ alanine aminotransferase (ALT) กลับสู่ค่าปกติสูงกว่า (ร้อยละ 76.4 และร้อยละ 69.8) พบการเกิด virological breakthrough ในกลุ่ม HBeAg positive มากกว่า HBeAg negative (ร้อยละ 23.6 และ 18.6) ไม่พบการบันทึกเหตุการณ์ไม่พึงประสงค์ที่พบบ่อยระหว่างการรักษา แต่พบเหตุการณ์ไม่พึงประสงค์ที่พบน้อยแต่มีความรุนแรง คือ การเกิด hepatitis flares จำนวน 6 ราย (ร้อยละ 6.1) และเกิด substantial biochemical change จำนวน 5 ราย (ร้อยละ 5.1) ไม่พบการหยุดยาหรือเปลี่ยนการรักษาจากการเกิดเหตุการณ์ไม่พึงประสงค์ที่รุนแรง ในการศึกษานี้พบการเพิ่มยาและเปลี่ยนยาในผู้ป่วยทั้งหมดร้อยละ 58.2 และร้อยละ 1.0 ตามลำดับ โดยส่วนใหญ่เป็นผู้ป่วยในกลุ่ม HBeAg positive และพบสัดส่วนการเพิ่มยาทีโนโฟเวียร์มากกว่าอะดีโฟเวียร์ ซึ่งเป็นไปตามข้อกำหนดการใช้ยาทีโนโฟเวียร์ที่ระบุไว้ในบัญชียาหลักแห่งชาติ **สรุป:** การใช้ยาลามิวูดีนในขนาด 150 มิลลิกรัมเพื่อเริ่มต้นการรักษาโรคไวรัสตับอักเสบเรื้อรังชนิดบี สามารถลดระดับของ HBV DNA ต่ำจนตรวจไม่พบ และ ALT กลับสู่ค่าปกติ แม้ว่ามีผู้ป่วยจำนวนน้อยเกิด HBe seroconversion และต้องมีการเพิ่มยาร้อยละ 58.2 ผลการศึกษาสะท้อนการใช้ยาการดูแลคนไข้

คำสำคัญ: ไวรัสตับอักเสบเรื้อรังชนิดบี, ลามิวูดีน, ผลลัพธ์ทางคลินิก

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Abstract

Objective: To evaluate clinical outcomes, adverse drug events and patterns of antiviral therapy from adding or changing medications during initial treatment with lamivudine for chronic hepatitis B (CHB) virus. **Method:** This retrospective descriptive study involved 98 patients with chronic hepatitis B who were treated with 150 mg lamivudine tablets at Maharaj Nakorn Chiang Mai Hospital from January 1st, 2005 to December 31st, 2009. **Results:** The 98 patients were divided into groups as 55 (56.1%) patients with HBeAg positive before the treatment, and 43 (43.9%) HBeAg negative. Patients with HBeAg positive had HBe seroconversion at 16.4% with HBV DNA below detection level and lower than HBeAg negative patients (18.2% and 53.5%); however, alanine aminotransferase (ALT) normalization was higher (76.4% and 69.8%). Virological breakthrough in HBeAg positive patients was higher than HBeAg negative patients (23.6% and 18.6%). Most common adverse drug events were not recorded during treatment but serious adverse drug events, hepatitis flares and substantial biochemical change were found in six (6.1%) and five patients (5.1%), respectively. No patients discontinued or changed their treatment as a result of serious adverse drug events. Adding and changing medication was carried out in 58.2% and 1.0% of patients respectively, who were mostly HBeAg positive. Patients added with tenofovir during lamivudine treatment were higher than those adding adefovir, which followed the terms of tenofovir as recorded in the National List of Essential Medicines. **Conclusion:** Our findings showed that use of lamivudine 150 mg as initial treatment for chronic hepatics B virus could achieve undetectable levels and ALT normalization, although a small number of patients had HBe seroconversion and 58.2% added other antivirals. The results reflects real-life practice.

Keywords: chronic hepatitis B, lamivudine, clinical outcomes

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Introduction

Hepatitis B virus (HBV) is a major global health problem. A systematic review in 2010 indicated that about 248 million individuals worldwide were chronically infected with HBV.[1] If cases remain untreated, 15 - 40% will develop liver cirrhosis or hepatocellular carcinoma [2, 3] which results on average in 1.4 million hepatitis patient deaths per year (roughly 687,000 deaths due to HBV and 704,000 due to HCV).[4]

Incidence of chronic hepatitis B (CHB) varies widely, with highest rates recorded in Asia- Pacific and sub- Saharan African regions where the disease is predominantly acquired during infancy or at a young age.[5] HBsAg prevalence prior to implementation of the HBV vaccination program was high (above 8%) in areas including mainland China, the Hong Kong special administrative region, Taiwan, Korea, Mongolia, the Philippines, Thailand, Vietnam, and the South Pacific island nations.[2] In Thailand, estimated prevalence was 5.1%, which translates to an estimated number of individuals with chronic hepatitis B living in Thailand in 2015 as high as three millions.[6] In addition, annual incidence rate of hepatocellular carcinoma is 38. 6 per 100,000 population for males and 17. 2 for females.[7]

Inhibition of viral replication by antiviral therapy for patients with chronic hepatitis B has been demonstrated to reduce the risk of progression and deterioration of liver disease and can even reverse liver fibrosis and initial cirrhosis.[8-10] Pegylated interferon therapy can be completed in 48 weeks and is not associated with the development of resistance; however, its use is limited by poor tolerability and adverse effects such as bone marrow suppression and exacerbation of existing neuropsychiatric symptoms such as depression. Oral nucleos(t)ide analog administration of recent nucleos(t)ide leads to effective, long- lasting suppression of HBV replication.[2,11,12] Currently, in Thailand, five oral nucleot(s)ides (i.e., lamivudine, adefovir, entecavir, telbivudine and tenofovir) have been approved by the Thai Food and Drug Administration (FDA) and three of these drugs including lamivudine, entecavir and tenofovir are on the National List of Essential Drugs 2018 (NLED).[13] Although many guidelines recommend the use of entecavir or tenofovir as initial therapy since they are less resistant[11,12], these suggestions have not been implemented in Thailand. The Thai Association for the Study of the Liver (THASL) [14] guidelines recommend the use of entecavir or tenofovir as the most appropriate drug for chronic hepatitis B patients; however, lamivudine is often the only readily available treatment option because it is the least expensive drug compared with entecavir or tenofovir in the NLED.

Lamivudine is characterized by good clinical tolerability, moderate antiviral efficacy, and quick resistance development. Randomized clinical trials of lamivudine compared with a placebo indicated that approximately 30% of patients treated with lamivudine developed resistance after 1 year[15] and 70% to 80% had developed resistance 5 years after the start of treatment.[16] However, in real-life practices, some patients who are on lamivudine therapy show good viral response which requires continuous follow- up to observe any development of lamivudine resistance.[17] Various situations are possible during clinical practice so real- life practice study makes data available to complement clinical trial studies.

Here, clinical outcomes, adverse drug events and patterns of antiviral therapy from adding or changing medications during initial treatment with lamivudine for the chronic hepatitis B virus were evaluated and summarized.

Methods

This retrospective study included 98 patients above 18 years old diagnosed with chronic hepatitis B who had detectable levels of HBV DNA before treatment and were taking lamivudine 150 mg tablets as initial treatment. Study duration was from January 2005 to December 2009 at Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand.

Patients with the following conditions were excluded from the study: those with coinfection with hepatitis C, hepatitis D, and human immunodeficiency virus, those with other forms of liver diseases such as alcoholic liver disease and autoimmune hepatitis, and those with previous treatment for HBV with interferon and nucleos(t)ide analogs other than lamivudine. Patients who did not have regular follow-ups on their medical records were also excluded.

Data were collected from hospital medical records using data abstraction form, developed by the researcher which consisted of 2 parts: general information and clinical information. Clinical outcomes were assessed by (i) serological response, defined as HBeAg loss with anti- HBe seroconversion in HBeAg positive chronic hepatitis B patients, (ii) biochemical response, defined as normalization of serum alanine aminotransferase (ALT) level at two consecutive measurements, (iii) virological response, defined as undetectable serum HBV DNA by polymerase chain reaction using COBAS AmpliPrep/CoBAS TagMan HBV test v2.0, with a lower limit of detection of 20 IU/ml, and (iv) virological breakthrough, defined as detectable viremia after complete virological suppression or a 1.0 log10 increase in viremia from on-treatment nadir.[2]

Evaluation of response to antiviral therapy and follow- up was conducted every six months using the following

parameters: serum ALT, HBsAg, HBeAg and anti- HBe. Patients who responded to treatment continued to receive lamivudine, while patients who developed breakthrough or did not respond to lamivudine were added to another oral nucleos(t)ide and their conditions were described in detail.

Safety

All adverse events were retrieved from the patients' medical records. These adverse events included common adverse events from lamivudine such as headache, fatigue, malaise, nausea and vomiting.[18] Serious adverse events were also evaluated including hepatitis flares, substantial biochemical changes, and hepatic decompensation. Hepatitis flares were defined as intermittent elevation of ALT to more than 5 times the upper limit of normal (ULN) (40 U/L) and more than twice the baseline value.[2] Substantial biochemical change was defined as increase in serum bilirubin to over 2 times ULN and/or PT 3 seconds longer than the baseline and out of the normal range, or with international normalized ratio (INR) above 1.5. Hepatic decompensation was defined as the occurrence of one or more of the following events: ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, variceal bleeding, or hepatic encephalopathy.[18]

Study protocol was reviewed and approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University (IRB No. 285/2015).

Statistical Methods

Descriptive statistics as mean with standard deviation and median with interquartile range (IQR) were calculated for interval variables, and counts with percentages for categorical variables using the SPSS 17.0 statistical software package.

Results

The study population consisted of 98 chronic hepatitis B patients (Table 1). There were slightly more patients who were HBeAg positive (55 patients or 56.1%) than those who were HBeAg negative (43 patients or 43.9%). Their mean age in years was 46.1 ± 13.7 and 50.0 ± 10.3 for HBeAg positive and HBeAg negative patients, respectively with over 80% as males in both groups. Before starting lamivudine treatment, 31 patients (56.3%) in the HBeAg positive group and 20 (46.5%) in the HBe negative group were having elevated ALT at above 2 times ULN. HBV DNA levels were detected in both groups at above 10^4 copies/mL (2,000 IU/mL). A similar proportion of patients (25%) in each group had cirrhosis (Table 1).

Table 1 Patient baseline characteristics (N = 98).

Characteristics	Number (%)	
	HBeAg positive	HBeAg negative
N (%)	55 (56.1%)	43 (43.9%)
Gender		
Male	45 (81.8%)	38 (88.4%)
Female	10 (18.2%)	5 (11.6%)
Age range (min – max)	19 - 77 years	
Age[a] (years)	47.8 (12.4)	
	46.1 (13.7)	50.0 (10.3)
HBV DNA[b] (copies/mL)	$1.2x10^7$	$1.1x10^6$
	($1.1x10^4$ - $6.3x10^7$)	($1.7x10^3$ - $4.0x10^7$)
Liver tests[b]		
ALT (U/L)	87 (21 - 572)	70 (30 - 436)
High normal	3 (5.5%)	3 (7.0%)
Minimally raised	21 (38.2%)	20 (46.5%)
Raised	31 (56.3%)	20 (46.5%)
Albumin (g/dL)	4.1(2.4 - 4.8)	4.1 (1.1 - 5.1)
Total bilirubin (g/dL)	0.9 (0.32 - 8.37)	0.9 (0.38 - 2.38)
Cirrhosis	14 (25.5%)	11 (25.6%)

[a] Mean (SD); [b] Median (IQR range);
Note: High normal: serum ALT between 0.5 and 1 x upper limit of normal (ULN) (40 IU/L); Minimally raised: serum ALT between ULN and 2 x ULN; Raised: serum ALT 2 x ULN; ALT = alanine aminotransferase; HBV = hepatitis B virus.

Out of the total 98 chronic hepatitis B patients, 40 (40.8%) received lamivudine monotherapy throughout the course of treatment, 13 (23.6%) were HBeAg positive and 27 (62.8%) were HBeAg negative. Of the remaining 58 patients, 46 were added with tenofovir and 11 with adefovir, and 1 patient were switched to tenofovir. Duration of treatment with lamivudine prior to adding/switching to other antivirals are shown as medians with ranges for the numbers of HBeAg positive and HBeAg negative patients in each group (Table 2).

Table 2 Pattern of antiviral therapy throughout the study (N = 98).

	HBeAg positive		HBeAg negative	
	N (%)	Time to event[c]	N (%)	Time to event[c]
Lamivudine	13 (23.6)		27 (62.8)	
Add tenofovir	34 (61.8)	24 (0 - 60 mo.)	12 (27.9)	36 (12 - 60 mo.)
Add adefovir	8 (14.5)	24 (12 - 48 mo.)	3 (7.0)	24 (6 - 30 mo.)
Switch to tenofovir	-	-	1 (2.3)	42[d]
Total	55		43	

[c] median (min - max), [d] at 42 months.

Reasons for adding other antiviral drugs including tenofovir and adefovir were virological breakthrough (n = 19), detectable HBV DNA at week 24 (n = 6), detectable HBV DNA at week 48 (n = 16), ALT elevation (n = 5), HBsAg elevation (n = 2) and HBeAg elevation (n = 2). The reason for one patient switching to tenofovir was a virological breakthrough and elevation of ALT and HBsAg at 36 months and 42 months, respectively.

Table 3 Clinical outcomes of lamivudine as initial treatment of HBeAg positive and HBeAg negative chronic hepatitis B (N = 98).

Parameter	HBeAg positive		HBeAg negative	
	No (%) N = 55	Time to event, month Median (min - max)	No (%) N = 43	Time to event, month Median (min - max)
HBeAg seroconversion	9 (16.4)[e]	25.9 (8 - 72)	-	-
HBsAg loss	2 (3.6)	24 and 48 mo.	0	-
HBV DNA below detection level	10(18.2)	24.0 (12 - 36)	23 (53.5)	20.3 (6 - 36)
ALT normalization	42 (76.4)	12.4 (6 - 42)	30 (69.8)	15 (6 - 42)
Flare of hepatitis B	-	-	2 (4.7)	18 and 24 mo.
Virological breakthrough	13 (23.6)	25.4 (6 - 48)	8 (18.6)	33 (36 - 60)

Note: HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e antigen.
[e] In lamivudine monotherapy.

Table 4 Cumulative treatment outcomes of antiviral therapy in HBeAg positive and HBeAg negative group at time points in months (N = 98).

	medication	HBeAg	N	Cumulative outcomes at time points in MONTHS					
				6	12	24	36	48	60
Serological response	LAM	Positive	13	0	1	5	7	7	7
		negative	27	-	-	-	-	-	-
	LAM+TNF	positive	34	0	1	0	2	2	2
		negative	12	-	-	-	-	-	-
	LAM+ADV	positive	8	0	0	0	0	0	0
		negative	3	-	-	-	-	-	-
HBV DNA below detection level	LAM	positive	13	0	1	5	7		
		negative	27	2	11	18	23		
	LAM+TNF	positive	34	0	3	3	3		
		negative	12	0	0	0	0		
	LAM+ADV	positive	8	0	0	0	0		
		negative	3	0	0	0	0		
ALT normalization	LAM	positive	13	5	12	13	13	13	13
		negative	27	6	12	24	19	19	20
	LAM+TNF	positive	34	10	18	23	24	24	24
		negative	12	3	6	8	8	9	9
	LAM+ADV	positive	8	3	3	3	4	4	5
		negative	3	1	1	1	1	1	1
Virological breakthrough	LAM	positive	13			0	0		
		negative	27			0	0		
	LAM+TNF[f]	positive	34			0	1		
		negative	12			0	0		
	LAM+ADV[f]	positive	8			1	1		
		negative	3			1	2		

Note: LAM = lamivudine, TNF = tenofovir, ADV = adefovir.
[f] Result after adding TNF or ADV.

Clinical outcomes of lamivudine as initial treatment in all patients are shown in Table 3. In the HBeAg positive group of 55 patients, 9 (16.4%) recorded HBeAg loss and became anti-HBeAg positive (serological response) with a mean of 25.9 months after starting the therapy. All of these patients were taking lamivudine monotherapy throughout the course of treatment. Two patients in the HBeAg positive group who were added with tenofovir were documented as HBsAg loss. Proportion of HBeAg negative patients with HBV DNA below the detection level was higher than the HBeAg positive group (53.5% vs 18.2%), while ALT normalization in the HBe positive group was more than the HBeAg negative group (76.4% vs 69.8%). However, virological breakthroughs were found in the HBeAg positive group at a higher proportion than the HBeAg negative group (23.6% vs 18.6%). Cumulative treatment outcomes of each antiviral therapy in the HBeAg positive and HBeAg negative groups are shown in Table 4.

Adverse events

No patients discontinued the treatment due to adverse events and no common adverse events were found in their medical records. Two patients (4.7%) in the HBeAg negative group flared up with hepatitis B, each at 18 and 24 months. Five patients (5.1%) had substantial biochemical change with a mean duration of 8.4 months (6 - 12 months).

Discussions and Conclusion

Lamivudine was the first oral nucleoside analog approved by the United States Food and Drug Administration (FDA) for the treatment of CHB in 1998 at a dose of 100 mg/d.[19] The Thai Association for the Study of the Liver (THASL) recommend lamivudine at 100 - 150 mg/day for patients who cannot afford entecavir or tenofovir as initial therapy.[14] Generally, a generic lamivudine 150 mg tablet is more often used than the original 100 mg tablets due to its low cost.

A total of 98 patients who started with a lamivudine dose of 150 mg daily as initial treatment were reviewed from electronic medical records with a 5-year follow-up period. From baseline characteristics, mean age of HBeAg negative patients was higher, while HBV DNA levels were lower than the HBeAg positive group. Similar results were found in other studies.[20,21] In addition, median HBV DNA levels in both groups were above 10^4 copies/ml (2,000 IU/ml), with 56.3% HBeAg positive and 46.5% HBeAg negative patients having a baseline ALT level above the upper limit of normal (ULN) (40 U/L). This met the European Association for the Study of the Liver (EPASL) criteria required to start treatment.[12] Some patients had ALT level before treatment at below 2 times ULN, thus they should not be treated with the drug according to Asia-Pacific clinical practice guidelines (APASL)[2] or the American Association for the Study of Liver Diseases (AASLD).[11] Indications for treatment might be considered by other factors such as serum HBV DNA levels, age older than 30, or severity of liver disease.[2,11,12]

We found that 40.8% of patients were able to use lamivudine monotherapy throughout the study without adding

or switching to other antivirals. Patients with HBeAg-negative were more likely to respond to lamivudine than HBeAg-positive patients, with more patients (62.8% vs 23.6%) able to use lamivudine as monotherapy and longer time to add tenofovir (at 36 months vs 24 months).

The remaining patients (58.2%) were added with other antivirals and the proportion of patients receiving tenofovir during treatment was the highest. Fewer patients in the HBeAg negative group were added with tenofovir (27.9% vs 61.8%) or adefovir (7% vs 14.5%). In addition, time taken before adding tenofovir was longer than for the HBe Ag positive group with a median of 36 months (range, 12 - 60 months) prior to drug addition. In one study, HBeAg positive patients with high viral load displayed high risk for developing drug resistance. Conversely, HBeAg negative patients showed a good response to lamivudine even with high viremia.[22]

The proportion of patients who added with tenofovir during the course of treatment was greater than those with adefovir. According to the National List of Essential Medicines (NELD), tenofovir is indicated for use in patients with HBV DNA levels greater than 1,000 copies/ml (or 200 IU/ml) after lamivudine treatment for 24 weeks.[13] The Thai Association guideline recommends that patients with lamivudine resistance be added with adefovir or tenofovir, or switched to tenofovir.[14] However, current clinical guidelines prefer switching to other antivirals (switch therapy) to continuing with lamivudine with added tenofovir.[2,11,12] Tenofovir disoproxil fumarate monotherapy has been shown to be effective in patients with lamivudine-, adefovir-, or entecavir-resistant HBV,[23] Here, only one patient switched to tenofovir after 36 months of lamivudine therapy. However, based on expert opinion, using tenofovir as the first-line drug would be the better option given that it has a very low resistance rate which reduces the time and cost of drug resistance management compared with providing lamivudine as the first-line drug.[24] At the time of our study, entecavir had not been included in the NELD. Use of the drug at high doses (1 vs. 0.5 mg daily) reduced the rate of resistance but was inferior to combination therapy of lamivudine plus adefovir or tenofovir monotherapy.[25,26]

The ideal endpoint for both HBeAg-positive and HBeAg-negative patients is sustained off-therapy HBsAg loss, with or without seroconversion to anti-HBs.[2,11,12] This is associated with a complete and definitive remission of CHB activity and an improved long-term outcome. This endpoint, however, is infrequently achievable with currently available anti-HBV agents[2], as seen in our study where two patients (3.6%) who continued lamivudine with tenofovir added had an HBsAg loss.

A more realistic endpoint is the induction of HBeAg loss, with or without anti-HBe seroconversion. This is a valuable endpoint in HBeAg positive CHB patients as it often represents partial immune control of chronic HBV infection.[12] In our study, 9 patients (16.4%) in the HBeAg positive group lost HBeAg and became anti-HBeAg positive (serological response) with a mean of 25.9 months after starting therapy. Interestingly, all of them used lamivudine as monotherapy. This finding concurred with Chang et al. who found that rate of HBeAg seroconversion was 18%.[27] However, this HBeAg seroconversion was lower than other studies in Chinese patients with CHB, Leung et al. found that after 3 years of continuous treatment with lamivudine 100 mg daily, 23 of 58 patients (40%) achieved HBeAg seroconversion.[28] Detailed analysis revealed that HBV DNA levels before treatment were high (7 log10), while low ALT levels in some patients may have lowered the response.

In terms of normalization of serum alanine aminotransferase (ALT) in our study, 76.4% in HBeAg positive patients and 69.8% in HBeAg negative patients had ALT normalization at median values of 12.4 months and 15 months, respectively. This finding was lower than those in other studies that found all patients (100%) had ALT normalization within 3 to 6 months.[16] For treatment of chronic hepatitis B at 6 months following 48 or 52 weeks of LAM 100 mg monotherapy, ALT normalization ranged from 41% to 72% in HBeAg positive and 71% to 79% in HBeAg negative patients.[12] Definition of ALT normalization varied among different trials and different guidelines. For example, definition of ALT normalization of AASLD defined by laboratory normal was 35 and 25 U/L for males and females, respectively.[11] APASL suggested the use of a conventional ALT level of 40 IU/ml rather than lower values of 30 and 19 IU/ml for males and females, respectively.[2]

In this present study, HBV DNA was below detection levels and the virological breakthrough rate was lower than other studies which reported higher rates of HBV DNA suppression and virological breakthrough after lamivudine therapy at week 24 or 52.[29-31] This may be because some patients did not

follow-up with HBV DNA during treatment because of the high costs while ALT is available throughout the course. Serial monitoring of HBV DNA levels is more important than any single arbitrary cut-off value in prognostication.[11]

Lamivudine has an excellent safety profile. Long-term study of up to 6 years showed no major adverse events or complications associated with lamivudine treatment.[18,32] Our study results found no common adverse events in patients' medical records. Two patients (4.7%) in the HBeAg negative group flared up with hepatitis B and 5 patients (5.1%) underwent substantial biochemical change.

The strengths of this study were the sufficient duration of follow-up and reflection on the effectiveness of drug therapy in the routine practice. However, certain limitations were found. The sample size was relatively small, therefore the power of analysis could be somewhat limited. With its retrospective design, comparisons with other drugs or with respect to certain characteristics could not be done. The resistance association regarding lamivudine could not be examined since no molecular investigation at the study setting was available. Even with these limitations, our results may provide important and more practical information on the clinical treatment of hepatics B virus in real-life practice and can be used as a basis data for further study. Further study is needed to determine patient characteristics with favorable greatest outcome from using lamivudine as initial treatment.

In conclusion, our study results demonstrated that the use of lamivudine 150 mg as initial treatment for CHB could achieve undetectable viral levels and ALT normalization, although small numbers of patients had HBe seroconversion and 58.2% were added with or switched to other antivirals.

Conflict of Interests

The authors declare no conflicts of interest regarding publication of this paper.

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