Original Article

Low Rate of Long-term Virological Suppression in Chronic Hepatitis B Patients Treated with Lamivudine

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Background: Hepatitis B virus (HBV) infection is one of the major global health problems which can lead to cirrhosis and hepatocellular carcinoma. Currently, main treatment for chronic hepatitis B (CHB) is oral nucleos(t)ide analogues (NA) such as lamivudine, entecavir, tenofovir and tenofovir alafenamide. Lamivudine (LAM) is the first agent and still widely used especially in resource-limited countries. LAM is safe and affordable, but the only drawback is high rate of drug resistance which is roughly 20% during first year of treatment.

Objective: To assess the rate of sustained hepatitis B virological suppression during long-term treatment with LAM in NA naive CHB patients.

Materials and Methods: This is a retrospective, single center study of adult chronic hepatitis B patients who were eligible for treatment according to treatment guideline. LAM was prescribed as the first treatment and must continue for at least 1 year. The patients were excluded if there were co-infected with hepatitis C virus or HIV, underlying hepatocellular carcinoma. Patient demographic data, liver biochemistries and HBV viral load were collected.

Results: There were 547 patients, 403 (73.7%) were male and 111 (20.3%) patients had cirrhosis at baseline which mostly Child-Pugh A (92/111, 86%). Two hundred and seventy-six patients (50.5%) were HBeAg-positive with mean age of 46.8 years. Cumulative incidence of sustained virological suppression defined as HBV DNA below detection was 98.7%, 69.8%, 47.4%, 30.6%, and 18.2%, at year 1, 2, 3, 4, and 5, respectively. In addition, in HBeAg positive CHB patients, 111/276 (40.3%) achieved HBeAg seroconversion and 1 (0.18%) had HBsAg loss. Factors associated with virological breakthrough included HBeAg positive and age >50 years old, tenofovir was added to rescue the patients who had virological breakthrough. No serious adverse event was seen.

Conclusion: Long-term treatment of CHB patients with LAM was sub-optimal. Rate of virological suppression was less than 20% at year 5. These patients must be monitored regularly, and rescued treatment added to prevent biochemical breakthrough. Treatment with high genetic barrier NA from beginning is advised to avoid unnecessary monitoring and the risk of virological breakthrough.

Keywords: Chronic hepatitis B, HBeAg positive, HBeAg seroconversion, Lamivudine, Oral nucleos(t)ide, Virological breakthrough

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Hepatitis B virus (HBV) infection is the major health problem, especially in developing countries like in Asia and Africa[1]. It is estimated that approximately 600,000 people die annually from chronic hepatitis B (CHB) related liver cirrhosis and hepatocellular carcinoma (HCC)[2]. The prevalence of CHB infection in Thailand is estimated to be about 4.5%, especially those born before introduction of HBV vaccine[3]. Current treatment of CHB consists of pegylated interferon and NAs, whereas most treatment nowadays are NAs which are easy to administer and fewer side effects. Currently, there are 6 NAs registered for treatment of CHB, including lamivudine (LAM, 100 mg/day), adefovir (10 mg/day) entecavir (0.5 and 1.0 mg/day), telbivudine (600 mg/day), tenofovir (TDF, 300 mg/day) and tenofovir alafenamide (TAF, 25 mg/day). However, most international guidelines[4-6] recommend only entecavir and TDF or TAF as first line agents since these NAs are among the most potent and have high genetic barrier to drug resistance. Nevertheless, lamivudine is still widely used in many countries including Thailand where LAM has been listed as first line agent for treatment of CHB[7]. Since CHB treatment usually requires long-term NAs and lamivudine is among low genetic barrier NAs with high rate of virological failure overtime, approximately 20% at first year[5]. This requires frequent HBV viral load monitoring to detect virological failure and to recue with TDF or TAF to prevent biochemical breakthrough and maintain the benefit of NA treatment. Since LAM is the first NAs and LAM study initially set for 1 year of treatment[8], long-term virological control of LAM is not well studied in real world setting because there were newer NAs with lower virological breakthrough available.

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The primary objective was to assess cumulative incidence of virological suppression during LAM treatment in real-world clinical practice of naive CHB patients and to determine rate of HBV viral control (HBV DNA <20 IU/mL) during treatment up to 5 years in naive CHB patients treated with LAM as well as HBeAg seroconversion in the patients with HBeAg positive and ALT normalization. Moreover, we would like to identify risk factors associated with virological breakthrough and adverse effect of lamivudine treatment. This information will be important to assess whether the use of LAM should still recommend as first choice NA in Thailand and many countries.

Materials and Methods

Study design

This retrospective study was conducted at Hepatitis Clinic, Siriraj Hospital from November 15, 2013 to October 31, 2014. The subjects were included if they were older than 18 years old with treatment indication (HBV DNA ≥2,000 IU/mL plus evidence of chronic hepatitis or cirrhosis), both HBeAg positive and negative at the baseline and have been treated with LAM for at least 1 year. The patients were excluded if there were co-infection with hepatitis C virus and/or human immunodeficiency virus, other causes of hepatitis, exposure to other nucleoside analogues active against HBV, evidence of decompensated cirrhosis, any malignancy, receiving immunosuppressive drugs, pregnancy or lactating women or creatinine clearance ≤50 mL/min at baseline. LAM dosing both 100 mg and 150 mg/day was included, and the study was approved by Siriraj Institutional Review Broad (Si. 654/2013).

Data collection

All demographic data, liver biochemistries, HBV DNA viral load were captured every 5 to 7 months. Treatment response is defined as HBV DNA maintained below 20 IU/mL with either normal or abnormal alanine transaminase (ALT). HBeAg seroconversion was defined as loss of HBeAg with presence of HBeAb. HBsAg was followed every year and LAM was discontinued if HBsAg became undetectable. HBV virological rebound was defined as >1 log IU/mL rebound, or HBV DNA >200 IU/mL from <20 IU/mL of HBV DNA measured twice at least one month apart. Adverse events were captured from patients records if it was mentioned related to LAM.

Statistical analysis

Descriptive statistics was reported as number and percentage for categorical variables and mean (standard deviation, SD) for continuous variables. Chi-square test, Fisher's exact test, Student t-test, or Mann-Whitney U test were used for statistical evaluation, where appropriate. Cox proportional hazards model was used to determine factors associated with virological breakthrough. All tests were two-sided and the threshold for statistical significance was established at a *p*-value <0.05. The statistical analysis was performed using SPSS version 13.0.

Results

There were 547 patients included in the present study. Baseline patient characteristics are shown in Table 1. Among LAM treated CHB patients, 403 (73.7%) were male and 111 (20.3%) had cirrhosis at baseline with mean age of 46.8 years and mean treatment follow-up of 33±22 months. Mean baseline HBV DNA was 4.82 million IU/mL and 276 patients were HBeAg-positive (50.5%), whereas 264 were HBeAg-negative (48.3%). After 5 years of follow-up, there were more patients who loss sustained virological control, especially after two years of treatment as shown in Figure 1. ALT normalization was 71.4%, 57.9%, 44.1%, 30.1%, and 24.8%, at year 1, 2, 3, 4 and 5, respectively. Patients with baseline HBeAg positive, HBeAg seroconversion achieved 108/268 (40.3%). We found that there was only 1 case (0.18%) of HBsAg loss in HBeAg positive who had HBeAg seroconversion during treatment period (Table 2). Factors associated with virological breakthrough included age ≥50 years and HBeAg (Table 3). There was no serious adverse event was demonstrated during long-term follow-up in naive patients receiving lamivudine treatment. No patient discontinued lamivudine due to side effects of the medication.

Discussion

This was a real-world retrospective study which included NA naive 547 CHB patients who were initially treated with LAM. The mean follow-up period was 32.7±22.0 months which represented either the time to last follow-up with virologically suppressed or before adding TDF or ADV. There were male predominant in our study which was like most of CHB studies. Rate of sustained virological suppression decreased over the period of treatment, as the result, there were more patients with virological breakthrough. This finding was similar to the study by Chang et al, where they found that cumulative rate of virological breakthrough was 17%, 40%, 57% and 67% after 1, 2, 3 and 4 years of LAM treatment, respectively[9]. Virological breakthrough can result in biochemical flare, sometimes follow by hepatic decompensation which can be

Table 1. Baseline characteristics of 547 patients

Parameters	Results
Age (years), mean (SD)	46.8 (11.9)
Male, n (%)	403 (73.7)
HBeAg status, n (%)	
HBeAg positive	276 (50.4)
HBeAg negative	264 (48.3)
Unknown	7 (1.3)
Cirrhosis, n (%)	111 (20.3)
Alcohol drinking, n (%)	99 (18.1)
HBV DNA (x10^6 IU/mL), mean (SD)	4.82 (16.94)
Duration of follow-up (months), mean (SD)	33 (22)

severe. It is essential that HBV DNA as well as patient compliance to the treatment must be reinforced frequently. However, HBV DNA cannot be done in many hospitals and it is costly which will make LAM is not a good candidate for the first line treatment in CHB patients. This is important finding since LAM is still widely used as first line treatment even all societal guidelines do not recommend for using as first line treatment because more potent and high genetic barrier NAs like entecavir, tenofovir and tenofovir alafenamide are now available[4-6]. These NAs can suppress HBV DNA with very low rate of virological breakthrough from 0 to 1.2%, moreover, there are generic which can be affordable. There was no correlation between sex, alcoholic drinking, cirrhosis, pretreatment HBV DNA with virological breakthrough. Baseline HBV DNA was 4.82 million IU/mL in our study and very high proportion of patients achieved initial virological control at first year, however, Hongthanakorn et al reported that failure to achieve undetectable HBV DNA was the only factors associated with virological breakthrough[11]. In this study we found that HBeAg-positive patients were more likely to develop virological breakthrough, this finding was also reported by Silva et al[10]. In CHB patients who were HBeAg positive, HBeAg seroconversion may predicted long-lasting suppression of HBV, reduced infectivity, and improved clinical prognosis and it is considered for treatment cessation endpoint. Our study found that 108/268 (40.3%) of HBeAg positive patients had HBeAg seroconversion with up to 5 years of LAM treatment.

There are several limitations in our study, firstly, this is a retrospective study where not all data can be captured. Secondly, drug compliance, which was important, was not systematically collected. Hongthanakorn C, et al had found that nearly 40% of virological breakthrough was not associated with NA resistance.

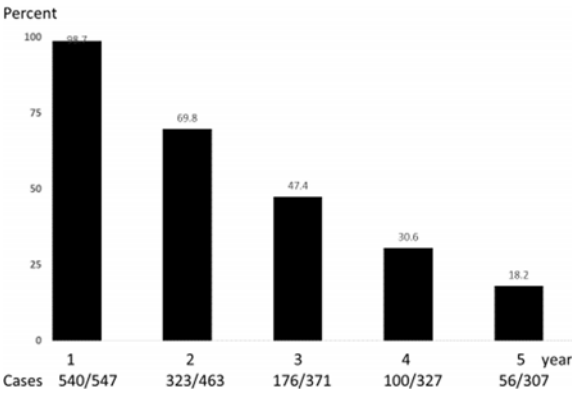

Figure 1. Virological response after treated with lamivudine (100 or 150 mg) for up to 5 years.

Conclusion

Long-term treatment of CHB patients with LAM is sub-optimal as rate of complete virological suppression decreased rapidly, especially after year 2 and only 18.2% remained HBV DNA suppressed at year 5. These patients must be monitored and rescued properly to prevent biochemical flare. Treatment initiation with high genetic barrier NA from the beginning is advised to avoid unnecessary monitoring and the risk of decompensation.

What is already known on this topic?

Treatment chronic hepatitis B with NAs usually continue with the same agent until virological breakthrough. LAM is the first NA used for HBV treatment and it is still popular in many parts of the world. The drawback of using LAM is viral breakthrough which was about 20% at first year but less data is known for long-term virological breakthrough.

What this study adds?

Using LAM is sub-optimal since rate of HBV DNA

Table 2. Outcome of lamivudine treatment in 547 chronic hepatitis B patients (mean follow-up time 33±22 months)

	Number (%)
ALT normalization	76 (24.8)
HBeAg seroconversion	108/268 (40.3)
HBsAg loss	1 (0.18)

ALT = alanine aminotransferase

Table 3. Factors associated with virological breakthrough

Factors	Odds ratio	95% confidence interval	*p*-value
Male	1.80	0.90 to 3.59	0.091
Age ≥50 years	1.79	0.99 to 3.20	0.05
Alcohol drinking	2.64	0.91 to 7.68	0.066
Cirrhosis	1.46	0.76 to 2.79	0.258
HBeAg positive	5.08	2.56 to 10.08	0.00
High HBV DNA (≥1x10^6 IU/mL)	1.83	0.65 to 5.19	0.249

viral suppression decreased rapidly when the time goes by. However, first year viral suppression in this study was higher than previous studies, may be due to low initial HBV DNA in our patients. LAM is not the good choice for first-line treatment since the cost of HBV DNA monitoring may be higher than the cost of generic, more potent, high genetic barrier NA.

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Conflicts of interest

The authors declared no conflict of interest.

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อัตราการกดไวรัสตับอักเสบบีเรื้อรังต่ำในผู้ป่วยไวรัสตับอักเสบบีเรื้อรังที่รักษาด้วยลามิวูดีน

สุพจน์ นิ่มอนงค์, ชาติชาย เศวตศิลา, ทวีศักดิ์ แทนวันดี

ภูมิหลัง: ไวรัสตับอักเสบบีเป็นปัญหาสาธารณะสุขที่สำคัญของโลกที่นำไปสู่ภาวะตับแข็งและมะเร็งตับปฐมภูมิ ในปัจจุบันการรักษาไวรัสตับอักเสบ บี เรื้องรังนิยมใช้ยารับประทาน nucleos(t)ide analogues (NA) เช่น ยาลามิวูดีน เอ็นติคาเวียร์ ทีโนโฟร์เวียร์และทีโนโฟเวียร์ อลาฟีนามายด์ ยาลามิวูดีนเป็น NA ตัวแรกและยังมีใช้อย่างแพร่หลายโดยเฉพาะในประเทศกำลังพัฒนา เป็นยาที่ปลอดภัย ราคาถูกแต่ปัญหาที่สำคัญ คือ อัตราการดื้อยาสูงโดยประมาณร้อยละ 20 แม้ในปีแรก

วัตถุประสงค์: เพื่อประเมินอัตราการกดไวรัสตับอักเสบ บี ด้วยยาลามิวูดีนในผู้ป่วยที่ได้รับยาลามิวูดีนรักษาไวรัสตับอักเสบบีเป็นระยะเวลานาน

วัสดุและวิธีการ: เป็นการศึกษาแบบย้อนหลังในสถาบันเดียวโดยการรวบรวมผู้ป่วยไวรัสตับอักเสบ บี เรื้อรังในผู้ใหญ่ที่มีข้อบ่งชี้ในการรักษาตามแนวทางการรักษา โดยผู้ป่วยได้รับการรักษาด้วยยาลามิวูดีนเป็นตัวแรกและได้รับต่อเนื่องอย่างน้อย 1 ปี ผู้ป่วยจะถูกคัดออกหากมีการติดเชื้อไวรัสตับอักเสบ ซี หรือไวรัสเอดส์หรือมีมะเร็งตับปฐมภูมิ จะมีการบันทึกข้อมูลส่วนบุคคล การทำงานของตับและปริมาณของไวรัสตับอักเสบ บี

ผลการศึกษา: มีผู้ป่วยทั้งหมด 547 ราย โดย 403 ราย (ร้อยละ 73.7) เป็นเพศชาย 111 ราย (ร้อยละ 20.3) มีภาวะตับแข็งตั้งแต่เริ่มการรักษา โดย 92 ราย (ร้อยละ 86) เป็น Child-Pugh A ผู้ป่วย 278 ราย (ร้อยละ 50.5) มีภาวะ HBeAg บวกและอายุเฉลี่ย 46.8 ปี อัตราการกดไวรัสตับอักเสบ บี สะสม โดยยังสามารถกดไวรัสตับอักเสบ บี ได้ต่ำกว่าเกณฑ์การตรวจพบปีที่ 1, 2, 3, 4, 5 เป็นร้อยละ 98.7, 69.8, 47.4, 30.6 และ 18.2 ตามลำดับ ในผู้ป่วยที่ HBeAg บวกพบว่า 111 (ร้อยละ 40.3) ได้ HBeAg seroconversion โดยผู้ป่วย 1 รายมี HBsAg ลบ ในผู้ป่วยที่มีระดับไวรัสสูงขึ้น ขณะได้รับยา จะได้รับการรักษาด้วยยาทีโนโฟร์เวียร์ และไม่พบอาการข้างเคียงของการใช้ยาลามิวูดีน

สรุป: การรักษาไวรัสตับอักเสบ บี เรื้อรังด้วยยาลามิวูดีนได้ผลต่ำกว่าความคาดหมาย เนื่องจากอัตราการกดไวรัสที่ 5 ปี เหลือน้อยกว่าร้อยละ 20 นอกจากนั้นผู้ป่วยยังต้องได้รับการติดตามตลอดเพื่อจะได้เปลี่ยนยาได้ทันก่อนการกำเริบของภาวะตับอักเสบ การเริ่มการรักษาไวรัสตับอักเสบ บี เรื้อรังด้วยยาที่มีการดื้อยาน้อยเหมาะสมกว่าและทำให้ไม่ต้องติดตามผู้ป่วยบ่อย ๆ