Original Article

Lamivudine Switching after Undetectable HBV DNA is Associated with High Rate of Virological Rebound in Entecavir-treated Chronic Hepatitis B Patients

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Objective: Current treatment of chronic hepatitis B includes oral nucleos[t]ides analogs which aim to suppress HBV DNA in order to prevent HBV related complications and the treatment is likely to be lifelong. With the implementation of Thai National list of essential medicine in late 2012, there are only lamivudine and tenofovir listed for treatment of chronic hepatitis B which can be reimbursable. Many patients treated previously with high genetic barrier drug like entecavir had been switched to lamivudine. This study aimed to investigate the outcome of lamivudine switching versus continuing entecavir in entecavir-treated chronic hepatitis B patients who were undetectable HBV DNA at the time of switching.

Materials and Methods: This is a retrospective and prospective cohort design. The patients who were switched to lamivudine as reimbursement policy were matched with similar patients who have continued entecavir. HBV DNA, liver biochemistry as well as clinical data were observed every 3 to 6 months for 2 years. Virological rebound was defined as detectable HBV DNA at least twice, one month apart.

Results: There were 73 chronic hepatitis B patients in both groups with similar baseline characteristics. The cumulative incidence of virological rebound was significantly higher in lamivudine-switching group as compared to entecavir-continuing group, 31.6% vs. 0% (p<0.001). The predictor for virological rebound in lamivudine-switching group was high baseline ALT. One hepatic decompensation was found in the patients who had virological rebound during study and the patient died. All breakthroughs were successfully rescued with tenofovir.

Conclusion: Switching from entecavir to lamivudine in the patients who have been treated with entecavir until undetectable HBV DNA was associated with high rate of virological breakthrough (31.6% at 2 years), even in the patients with low baseline HBV DNA. Switching to lamivudine is not safe since virological breakthrough can result in mortality. If practice lamivudine switching, closely monitor the patients and rescue as soon as virological breakthrough is detected.

Keywords: Lamivudine switching, Virological rebound, Undetectable HBV DNA, Entecavir-treated chronic hepatitis B

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Chronic hepatitis B virus infection affects almost 350 million people worldwide[1], it is a serious health burden which can lead to liver cirrhosis and its complication, hepatocellular carcinoma[2]. Treatment is aimed to eliminate or to suppress HBV DNA in order to limit disease progression[2]. Current treatment includes interferon-based and many oral nucleoside analogues (NAs) such as lamivudine (LAM), entecavir (ETV) and tenofovir (TDF)[3]. All of these NAs have demonstrated reduction of HBV DNA, normalization of ALT as well as improvement of liver histology in both HBeAg positive and negative[4,5]. Lamivudine, though has lower potency and higher virological breakthrough, but it is widely used as first line agent for the treatment of chronic hepatitis B, especially in resource-limited countries because of it is much lower cost.

With the implementation of a Thai national list of essential medicine in late 2012, there were only LAM as first-line agent and TDF; only LAM failure was listed for treatment of chronic hepatitis B in Thailand[6]. Many patients who had been treated with a high genetic barrier drug like ETV had been switched to LAM if they wanted to be reimbursable. It is not known whether virological response (undetectable HBV DNA) by a high potency drug like ETV can be maintained after switching to a less potency drug like LAM. One small study from Hong Kong, has shown that sequential therapy using ETV in HBeAg positive chronic hepatitis B with high baseline HBV DNA followed by LAM resulted in virological rebound in about 24%[7]. However, the predictors for virological rebound in LAM-switching group were not mentioned and there are no data in HBeAg negative chronic hepatitis B with lower baseline HBV DNA.

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In this study, we have investigated the outcome of LAM switching versus continuing ETV in ETV-treated chronic hepatitis B patients who were undetectable HBV DNA at the time of switching and to identify the predictors for virological rebound in LAM switching group.

Materials and Methods

Study population

This is a retrospective and prospective cohort study design conducted at Hepatitis Clinic, Siriraj Hospital, Thailand, during October 1, 2012 to December 31, 2014. The inclusion criteria were male or female, age ≥18-year, chronic hepatitis B infection (persistent HBsAg positive at least 6 months with HBV DNA ≥2,000 IU/ml consistent with treatment guideline). The patients were excluded if they were previously treated with LAM, known to have co-infection with HCV, HDV, or HIV, any previous malignancy including hepatocellular carcinoma, previous diagnosis of decompensated cirrhosis, and baseline eGFR of less than 50 mL/min. All patients were treated with ETV 0.5 mg daily and all patients had undetectable HBV DNA until enrollment.

The patients were divided into 2 groups. LAM-switching group included patients who were switched to LAM 100 mg daily as reimbursement policy. ETV-continuing group which included patients who were matched similar characteristics with switching group and continued ETV 0.5 mg daily. During follow-up at hepatitis clinic, clinical data, liver biochemistry and HBV DNA were observed every 3 to 6 months for 2 years. Liver biochemistry and HBV DNA measurement were performed in Siriraj laboratory center and all patients were consented and informed about treatment compliance. The study was approved by Siriraj IRB.

Withdrawal or termination criteria

If there were new detectable HBV DNA >1,000 IU/ml, clinical or laboratory evidence of liver decompensation, evidence of hepatocellular carcinoma, death or loss to follow up, these patients would be withdrawn from the study and appropriate treatment would be given.

Outcome

The primary outcome was the cumulative incidence of virological rebound which was defined as detectable HBV DNA at least twice, one month apart. The secondary outcome was predictors for virological rebound in LAM-switching group.

Statistical analysis

All analysis was performed using IBM SPSS Statistics version 20.0. Categorical variables were analyzed using the Chi-square test or Fisher's exact test when appropriate. Continuous variables with normal distribution were expressed as mean, standard deviation and analyzed using the Independent-samples t-test. Other continuous variables were expressed as median and interquartile range and analyzed using the Mann-Withney U test. The *p*-values <0.05 were considered statistically significant.

Results

Baseline characteristics

Total of 73 chronic hepatitis B patients were recruited into our study. There were 38 patients in LAM group (LAM-switching group) and 35 patients in ETV group (ETV-continuing group). Patients' characteristics were shown in Table 1. All baseline characteristics and laboratory data of 2 groups were not different, although there was higher baseline HBV viral load in LAM group but that did not reach statistically significance. We observed significantly lower mean serum albumin in LAM group as compared to ETV group ($p = 0.012$) but both values were within normal limits.

Cumulative incidence of virological rebound

After 24-month follow-up, detectable HBV DNA was founded in 12 patients (31.6%) in LAM group and none (0%) in ETV group. The cumulative virological rebound incidence was significantly increased in LAM group as

Table 1. Baseline characteristics and laboratory data between two groups

Characteristics	LAM group (n = 38)	ETV group (n = 35)	*p*-value
Age (years), mean ± SD	54.8±10.3	55.3±9.0	0.81
Male, n (%)	22 (57.9)	24 (68.6)	0.35
Smoking, n (%)	2 (8.7)	2 (12.5)	1.000
Alcoholic consumption, n (%)	4 (16.0)	3 (11.5)	0.88
Hypertension, n (%)	14 (36.8)	12 (34.3)	0.82
Diabetes mellitus, n (%)	6 (16.7)	2 (6.5)	0.27
Cirrhosis, n (%)	6 (15.8)	8 (22.9)	0.44
HBeAg positive, n (%)	8 (21.1)	9 (25.7)	0.64
Baseline HBV viral load (million IU/mL), median (range)	1.06 (0.007 to 11)	1.18 (0.002 to 9.4)	0.99
eGFR (mL/min/1.73 m^2), mean ± SD	79±21	72±12	0.11
ALT at switching (U/L), mean ± SD	23±12	25±11	0.52
Albumin (g/dl), mean ± SD	4.4±0.3	4.6±0.3	0.01
ETV treatment before enrollment (years), median (range)	3.1 (0.1 to 6.4)	2.6 (0.4 to 5.6)	0.64

BMI = Body mass index, ETV = Entecavir, LAM = Lamivudine, VL = Viral load

compared to ETV group, as shown in Figure 1.

Among 12 patients in LAM group with virological rebound at 24 months, one patient was associated with acute HBV flare at 18th month after switching. He had progressive jaundice and liver decompensation, his HBV DNA was 184,341 IU/mL at the time of virological rebound. There was also biochemical flare (total bilirubin 21.6 mg/dL, direct bilirubin 14.83 mg/dL, AST 1,455 U/L, ALT 961 U/L, with MELD score of 25). The patient was admitted and TDF was added to LAM while on waiting list for liver transplantation. Unfortunately, he died from hepatic decompensation and complications. Eleven patients were successfully rescued with TDF. Patient's characteristics in rebound group were summarized in Table 2.

The cumulative incidence of virological rebound at 12 months increased significantly in LAM-switching group as compare to ETV group (15.79% vs. 0% for LAM and ETV group respectively, $p = 0.026$). Although the virological rebound in LAM group was observed as early as 3 months after switching, most virological rebound occurred after 1 year of switching.

Predictors for virological rebound in LAM group

After subgroup analysis in LAM group, the predictors for virological rebound at 24th month were found, as shown in Table 3 and Table 4. Higher median baseline HBV DNA, higher ALT and lower serum albumin in rebound group were statistically significant predictors of rebound (*p*-value = 0.041, 0.024, 0.029 respectively). There was no predictor for LAM failure; however, baseline HBV DNA of greater than 1.0 million IU/mL was nearly significant predictor (OR = 4.1 [0.9 to 18.7], $p = 0.061$). Other parameters such as cirrhosis, HBeAg positive and longer treatment with ETV were not statistically significant.

All significant predictors were included to analyze

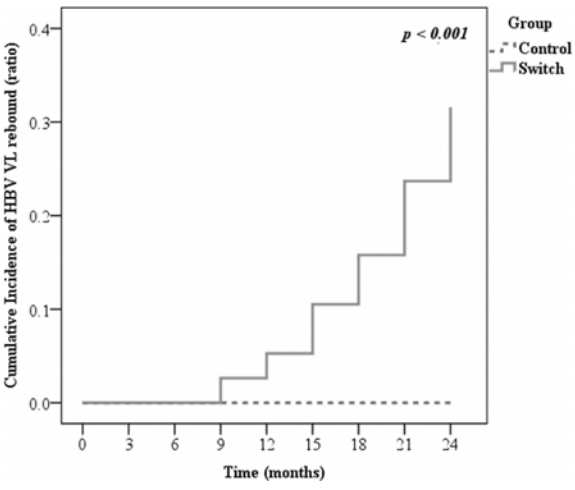

Figure 1. Kaplan-Meier plot of cumulative incidence of virological rebound between 2 groups.

Table 2. Patient's characteristics in LAM rebound group

No.	Age (years)	Sex	HBeAg	Cirrhosis	Pre-ETVHBV DNA (IU/mL)	ETV treatment time before switching (years)	Undetectable DNA before switching (years)	LAM switching time before VR (months)	Rescue treatment	Outcome
1	69	M	Neg	No	103,000	1.33	0.92	15	TDF + LAM	Suppression
2	55	M	Neg	No	230,000	5.58	6.42	18	TDF + LAM	Suppression
3	52	M	Neg	Yes	379,000	2.83	0.06	12	TDF + LAM	Suppression
4	53	M	Neg	No	1,040,000	6.00	4.42	9	TDF + LAM	Suppression
5	63	M	Neg	Yes	1,630,000	6.50	5.17	21	TDF + LAM	Suppression
6	50	F	Neg	No	3,360,000	2.25	1.33	12	TDF + LAM	Suppression
7	30	M	Pos	No	3,400,000	2.17	0.08	21	TDF	Suppression
8	62	F	Neg	No	7,340,000	5.42	3.58	21	TDF + LAM	Suppression
9	51	F	Pos	No	8,540,000	4.67	3.75	18	TDF	Suppression
10	61	F	Neg	No	10,300,000	4.50	2.67	15	TDF + LAM	Suppression
11	60	M	Neg	Yes	14,800,000	5.00	4.08	18	TDF + LAM	Death
12	49	M	Pos	No	>38,000,000	5.53	2.83	6	TDF + LAM	Suppression

ETV = Entecavir, LAM = Lamivudine, TDF = Tenofovir, VR = Virological rebound

by univariate and multivariate analysis, as shown in Table 5. Only high baseline ALT was still significant predictor (OR = 1.19 [1.00 to 1.41], p = 0.045). We again found that high baseline HBV DNA higher 1.0 million IU/mL almost reached statistical significance (OR = 13.85 [0.93 to 205.76], p = 0.056).

Discussion

Currently, there are few data for switching therapy from high potency, low resistance NA to low potency agents in chronic hepatitis B treatment after undetectable HBV DNA. In present study, we have evaluated the efficacy of LAM-switching in ETV-treated chronic hepatitis B patients who had optimal viral suppression compared to continuing ETV in term of HBV DNA viral suppression. We hypothesized that lower potency drugs like LAM could not maintain adequate viral suppression which occurred earlier as a result of treatment with a higher potency agent like ETV even in the patients with lower baseline HBV DNA[4,5]. This was based on previous study which showed that LAM switching was associated with higher virological rebound rate in chronic hepatitis B, HBeAg positive[7].

This study has shown that the cumulative incidence of virological rebound at 24 months was much higher in LAM group as compared with those who had continued ETV. Virological rebound was observed mainly after 1 year of switching and continued to increase. In ETV continue group, we did not observe any virological rebound. In the patients who had virological rebound, rescue treatments with TDF either TDF add-on or switching can successfully suppress HBV DNA in all patients. However, one patient died due to liver decompensation.

We found that in LAM group with virological rebound, higher baseline HBV DNA and ALT at the time of switching appeared to associate with virological rebound but did not reach statistically significant. Higher baseline HBV DNA was also associated with LAM treatment failure in previous study[8].

This is the first study demonstrated that LAM switching was not safe in the patients who had successfully suppressed with ETV, even in the patients who had long period of virological suppression before switching or the patients with low baseline HBV DNA. Switching is dangerous especially in the patients who had cirrhosis at the baseline which can result in mortality. Compliance was one of the important factors that influenced virological rebound, in both groups; the patients were treated in clinic where compliance was enforced in every visit.

However, there were some limitations in our study since randomization could not perform but we have tried to match patients with similar demographic and laboratory data between two groups.

Conclusion

Switching from ETV to LAM in chronic hepatitis B patients who have been successfully treated with ETV until HBV DNA undetectable is not safe. High rate of virological breakthrough was observed as high as 31.6% at 2 years, especially the patients who had high baseline HBV DNA or high ALT before treatment commence. If switching was practiced, these patients must be followed carefully to detect viral breakthrough as early as possible and rescue treatment must be added promptly in order to prevent hepatic

Table 3. The predictors for virological rebound at 24th months

Predictors	Odds ratio (95% CI)	p-value
Cirrhosis	2.6 (0.4 to 15.1)	0.36
HBeAg positive	1.4 (0.3 to 7.1)	0.69
Baseline HBV DNA ≥1.0 million IU/mL	4.1 (0.9 to 18.7)	0.06

Table 4. The predictors for virological rebound at 24th months

Predictors	Rebound group	Non-rebound group	p-value
Baseline HBV DNA (million IU/mL), median (range)	5.35 (0.10 to 110)	0.39 (0.01 to 110)	0.04
ALT (U/L), mean ± SD	30±14	20±10	0.02
Albumin (g/dL), mean ± SD	4.2±0.3	4.5±0.2	0.03
Post-ETV VL suppression time (years), median (range)	3.2 (0.5 to 6.4)	3.1 (0.1 to 5.6)	0.89

ETV = entecavir, VL = viral load

Table 5. Univariate and Multivariate analysis of predictors for virological rebound at 24th month

Predictors	Univariate analysis odds ratio (95% CI)	Multivariate analysis odds ratio (95% CI)	p-value
Baseline HBV DNA ≥1.0 million IU/mL	4.09 (0.89 to 18.72)	13.85 (0.93 to 205.76)	0.06
ALT (U/L)	1.07 (1.01 to 1.14)	1.19 (1.00 to 1.41)	0.05
Albumin (g/dL)	0.04 (0.01 to 0.85)	0.002 (0.001 to 1.152)	0.06

decompensation.

What is already known on this topic?

Treatment of chronic hepatitis B with NAs usually continues with the same agent until virological breakthrough. It is not known whether switching from higher potency NA after virological suppression to lesser potency NA can maintain virological control.

What this study adds?

Switching ETV to LAM had high rate of virological breakthrough was observe as high as 31.6% in 2 years. It is not advisable since some will result in severe biochemical flare and will limit selection of future NAs.

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Potential conflicts of interest

The authors declare no conflict of interest.

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