Original Article

Two-year Efficacy of the Real World Roadmap Concept for Lamivudine Therapy in Chronic Hepatitis B Patients at Songklanagarind Hospital

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Objective: The roadmap concept of adding-on non-cross resistance antiviral therapy for chronic hepatitis B patients who do not achieve an early virological response at week 24 after treatment was introduced in 2007; aiming to improve long-term viral suppression rate. However, the clinical data to prove this concept are still scarce. This study is to evaluate 2-year efficacy of this approach applied to the real world practice of lamivudine therapy.

Materials and Methods: The data of adult chronic hepatitis B patients in Songklanagarind Hospital from 2004 to 2011 were retrospective analyzed. Inclusion criteria were patients on lamivudine monotherapy at baseline and having regular follow-up for ≥2 years. Exclusion criteria were patients with coinfection with hepatitis C and/or human immunodeficiency virus, coexisting malignancy, co-prescription with immunosuppressant(s), and pregnancy. Patients who received treatment modification at week 24 were classified as the roadmap group [RG] and the remaining patients were the conventional group [CG]. Treatment outcomes were measured at week 96 in terms of virological response, virological breakthrough, and biochemical response rates.

Results: Of the 3,551 chronic hepatitis B patients during the study period, a total of 253 patients were eligible for the study. Seventy-seven patients (30.4%) were classified as the RG and 176 patients were in the CG. At week 96, patients in the RG achieved a significantly higher rate of undetectable virus compared with the CG (83% vs. 63%, $p = 0.002$), and less virological breakthrough (17% vs. 32%, $p = 0.017$). Biochemical response was also high (92% vs.78%, $p = 0.066$).

Conclusion: Lamivudine therapy with the application of the roadmap concept is an effective approach for chronic hepatitis B treatment in real world practice.

Keywords: Efficacy, Hepatitis B, Lamivudine, Roadmap, Treatment

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Chronic hepatitis B infection is one of the major worldwide health problems, especially in the countries of Southeast Asia, including Thailand, in which the prevalence is about 3% to 5%[1]. Hepatitis B is a leading cause of cirrhosis, liver cancer, and liver-related death.

Lamivudine is the first nucleoside analog that was approved for treatment of chronic hepatitis B infection. The clinical benefits of lamivudine treatment have been confirmed by a number of studies in terms of HBV DNA suppression, ALT normalization, and liver histological improvement[2,3]. The drawback of lamivudine treatment is the high rate of resistance, as of 70% resistance rates were found after 4 years of treatment with lamivudine[4]. The newer agents, such as entecavir and tenofovir, with more viral suppression

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potency, and lower resistance rates compared with lamivudine, were subsequently introduced to the market. The long-term clinical outcomes after treatment with these new agents were also proven by clinical trials[8-10]. Currently, the American and European guidelines recommend using entecavir or tenofovir as the first line therapy for chronic hepatitis B patients[3,6,7]. However, due to the much higher cost of new antiviral agents, lamivudine treatment is still the first line therapy in Thailand and many countries in Asia, due to patient reimbursement policies.

The previous studies showed that a HBV DNA level of less than 200 IU/mL at week 24 after the administration of antiviral therapy is a significant predictor of good long-term outcome and low risk of lamivudine-resistance[11-14]. The roadmap concept of antiviral treatment in chronic hepatitis B patients, using the level of HBV DNA at week 24 after antiviral agent initiation to decide further treatment, was introduced in 2007[15]. Its aim is to improve long-term virological suppression and lower resistance rates of antiviral therapy with low genetic barrier agents. The roadmap concept suggests adding-on non-cross resistance second agents if the HBV DNA level at week 24 is still detectable in patients who were treated with low-genetic barrier agents, including lamivudine. This concept is widely accepted and followed by many physicians in Thailand, but clinical data confirming the efficacy of this concept is still scarce.

This study was conducted in order to evaluate the 2-year efficacy of the roadmap concept when applied to the real world practice of lamivudine therapy.

Materials and Methods

Study population

The present study was a retrospective single center study, approved by Human Research Ethics Committees [HREC] at Faculty of Medicine, Prince of Songkla University. The study population was chronic hepatitis B patients who were treated with lamivudine therapy and followed-up regularly at Songklanagarind Hospital (Prince of Songkla University, Hatyai, Songkhla, Thailand) from 2004 to 2011. Inclusion criteria were: patients aged of at least 18 years old who were diagnosed with chronic hepatitis B infection, coded from hospital database by ICD-10 (International Classification of Disease coding-10), were nucleos(t)ide analog naive and treated initially with lamivudine monotherapy, and followed-up regularly at the hospital's out-patient clinic ≥96 weeks. Exclusion criteria were prior interferon treatment within 24 weeks, pregnancy, coexisting malignancy, HIV or hepatitis C coinfection, and were on immunosuppressive agent(s).

Study protocol

All patients diagnosed with chronic hepatitis B in Songklanagarind Hospital database from 2004 to 2011 were retrospectively reviewed according to inclusion and exclusion criteria. The eligible patients were included in the study. Patients who had HBV DNA level at week 24 (±4 weeks) time point after lamivudine treatment and 1) continued lamivudine monotherapy if HBV DNA level was <200 IU/mL, or 2) received add-on therapy to adefovir, or add-on/switch therapy to tenofovir, or switch therapy to entecavir 1 mg/day, if HBV DNA level at week 24 was more than 200 IU/mL were classified as the roadmap concept group. The remaining patients, which treatment modification was not applied when HBV DNA level at week 24 was >200 IU/mL, were classified as the conventional group.

Baseline characteristics including, but not limited to, gender, age, HBeAg status, initial viral load, alanine aminotransferase [ALT] level, and cirrhotic status were obtained. Biochemical, and virological data during lamivudine treatment until 96 weeks were recorded and analyzed.

Study outcomes

The primary outcome of this study was complete virological suppression rates at week 96 of lamivudine treatment. The secondary outcomes were biochemical response rates, biochemical breakthrough rates, virological breakthrough rates, and clinical breakthrough rates of patients in the roadmap concept compared with conventional group.

Definition of terms

According to the American Association for the Study of Liver Diseases [AASLD] guidelines 2009[6] and Asian Pacific Association for the Study of the Liver [APASL] guidelines 2012[5], the definitions of terms were as follows:

Complete virological suppression: decrease in serum HBV DNA to undetectable levels by polymerase chain reaction [PCR]-based assays.

Biochemical response: decrease in serum ALT to within the normal range.

Biochemical breakthrough: increase in ALT above the upper limit of normal after achieving normalization, during continued treatment.

Viral breakthrough: increase in serum HBV DNA by 1 log 10 IU/mL (10-fold) above nadir after

achieving virological response, during continued treatment.

Clinical breakthrough: fulfill criteria of biochemical and virological breakthrough.

Statistical analysis

Baseline descriptive data were expressed as mean and standard deviations for continuous variables and as percentages for discrete variables. Comparisons between the two groups were assessed by Student t-test for continuous data. Proportional data were assessed by Chi-square test or Fisher's exact test. A *p*-value of less than 0.05 was considered statistically significance.

Results

Of the 3,551 patients diagnosed with chronic hepatitis B infection duringthe study period, 3,298 patients met the exclusion criteria and the remaining 253 patients were included in this study. Seventy-seven patients (30.4%) were classified as the roadmap group and 176 patients were in the conventional group (Figure 1).

The baseline characteristics between the roadmap group and conventional group were comparable (Table 1). The majority of patients were male, with an initial viral load of less than 8 log IU/mL. Cirrhosis and HBeAg positive presented in about half of the patients.

During the 96 weeks of follow-up, 21 patients (27%) in the roadmap group received treatment modification, the second agent was added in 17 patients (7 for tenofovir and 10 for adefovir), and 4 patients were switched to other medications (2, 1, and 1 patients for tenofovir, adefovir, and entecavir, respectively). In the conventional group, treatment with antiviral agent(s) was eventually modified after 24 weeks of treatment in 40 patients (22.7%).Among the conventional group, the addition of tenofovir was observed in 15 patients, adefovir in 15 patients, and switched therapy was observed in 10 patients (1, 1, and 8 patients for tenofovir, adefovir, and entecavir, respectively).

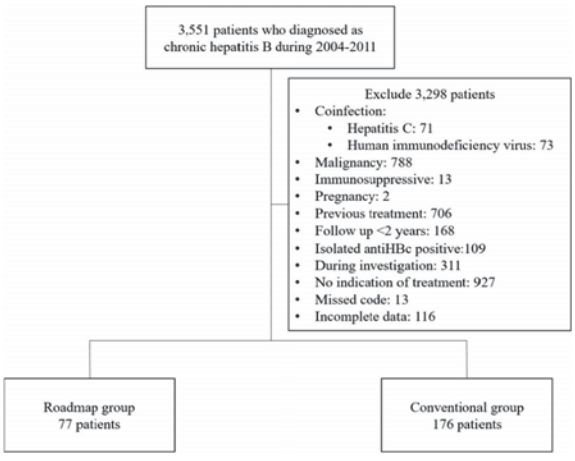

Figure 1. The study population.

At week 96, patients in the roadmap group achieved a significantly higher rate of undetectable virus (complete virological response) of more than 80% compared with the conventional group, lower virological breakthrough, and lower biochemical breakthrough were also observed. The biochemical response rate was also high in the roadmap group and less clinical breakthrough was observed in the roadmap group but statistical significance was not reached (Table 2). Moreover, the proportion of detectable virus in the roadmap group was consistently higher than in the conventional group throughout the study period.

Discussion

The present study is the first proof-of-concept study for the application of the roadmap concept to lamivudine therapy in realworld practice. Our study showed that more than 80% of patients in the roadmap group achieved undetectable virus at 2 years, which is much higher than lamivudine monotherapy treatment data from previous studies, as only 26 to 74% achieved complete virological suppression[4,16,17]. ALT normaliza tion at 2 years after treatment was more than 90%.

When compared with other studies of the roadmap concept in clinical trial settings, we demonstrated that the realworld efficacy of the roadmap concept in lamivudine therapy is similar to the telbivudine-roadmap approach, in which a 76.7% undetectable rate at 2 years was observed[18]. However,the virological response rate in our study (83% in the roadmap group and 63.1% in the conventional group) seems to be higher than in a recently published study of lamivudine therapy by Liang et al[19], which was 48.3% in OPTIMIZE arm (comparable to our study's roadmap group) and 34.8% in MONO arm (comparable to our study's conventional group). The most probable reason of higher undetectable virus rates at 2 years in our study may be the influence of lower initial viral loads, as we know that higher baseline HBV DNA is a predictor of lamivudine resistance and lower virological response rates in the long-term.

Table 1. Baseline characteristics of patients in the conventional group and the roadmap group

Parameters	Conventional group (n = 176)	Roadmap group (n = 77)	*p*-value
Gender			1.000
Male	109 (61.9)	48 (62.3)	
Female	67 (38.1)	29 (37.7)	
Age (years), mean (SD)	46.4 (13.5)	48.3 (12.2)	0.277
BMI (kg/mm^2), median (IQR)	23.4 (21 to 25.8)	23.8 (21 to 26.1)	0.625
Initial HBV DNA (IU/mL), median (IQR)	566,500 (59,150 to 2,598,393.5)	780,000 (111,000 to 3,800,000)	0.467
Initial HBV DNA			1.000
<8 log IU/mL	167 (94.9)	73 (94.8)	
≥8 log IU/mL	9 (5.1)	4 (5.2)	
Cirrhosis	69 (41.8)	32 (42.7)	1.000
HBeAg			0.356
Positive	98 (56.6)	37 (49.3)	
Negative	75 (43.4)	38 (50.7)	
ALT (U/L), median (IQR)	64.5 (39 to 116.8)	56 (38 to 116)	0.492
Cr (mg/dL), median (IQR)	0.9 (0.8 to 1)	0.9 (0.8 to 1)	0.431
Diabetes mellitus	12 (6.8)	6 (7.8)	0.991
Hypertension	9 (5.1)	7 (9.1)	0.265
Dyslipidemia	5 (2.8)	6 (7.8)	0.095

ALT = alanine aminotransferase; BMI = body mass index; Cr = creatinine; HBV DNA = hepatitis B virus deoxyribonucleic acid; IQR = interquartile range; SD = standard deviation

Table 2. Treatment outcomes at week 96 between the conventional group and the roadmap group

Outcomes	Conventional group (n = 176)	Roadmap group (n = 77)	*p*-value
HBV DNA level at week 96			0.002
Undetectable	111 (63.1)	64 (83.0)	
Detectable	65 (36.9)	13 (17.0)	
Biochemical response at week 96			0.066
Response	101 (78.3)	44 (91.7)	
Non-response	28 (21.7)	4 (8.3)	
Virological breakthrough			0.017
No	119 (67.6)	64 (83.1)	
Yes	57 (32.4)	13 (16.9)	
Biochemical breakthrough			0.041
No	137 (77.8)	69 (85.7)	
Yes	39 (22.2)	8 (14.3)	
Clinical breakthrough			1
No	163 (92.6)	72 (93.5)	
Yes	13 (7.4)	5 (6.5)	

HBV DNA = Hepatitis B virus deoxyribonucleic acid

When looking at the data of high-genetic barrier agents, we found that our roadmap group patients achieved the more desirable outcome of complete virological suppression at year 2 of treatment, which is higher than in adefovir monotherapy (50%), and similar to high-potency agents which are recommended by the American and European guidelinesas the preferred first line treatment, i.e.

entecavir (74% to 79%), and tenofovir (98% to 99%)[20,21]. Even though this was not a head-to-head comparison study, our data showed that in developing countries, where low-genetic barrier agents are still the first line option, starting with non-expensive, low-genetic barrier agents, followed by add-on therapy at the proper time according to the roadmap concept, can result in favorable long term treatment outcomes at 2 years and might be comparable to entecavir or tenofovir monotherapy. This result is concordant with the recently published study, the cost effective model in Asia Pacific, which suggested that using the lamivudine-roadmap approach and add-on with tenofovir is the most cost-effective approach for Thai patients[22].

The limitation of our study was the incomplete data at some points in time as it is a retrospective study in nature, e.g. when biochemical breakthrough was observed, we could not precisely identify the cause of ALT elevation (no complete data of viral serology or history of other medications and herbal use). If accompanying HBV DNA was also high at the time of biochemical breakthrough, either lamivudine-resistance or non-compliance were possible causes as we did not perform viral resistance testing for confirmation and sometimes compliance data were not noted. Another limitation was that only few patients underwent HBeAg, anti HBe, HBsAg, and anti HBs testing at each time point, thus, we could not analyze serological response rates.

Finally, this study confirmed the better efficacy of the lamivudine-roadmap approach in chronic hepatitis B patients over the conventional approach in terms of virological suppression and biochemical normalization outcomes at 2 years after treatment. Nevertheless, a long-term study is still needed in order to compare clinical outcomes, such as progression to cirrhosis and hepatocellular carcinoma occurrence rates, between these 2 treatment strategies.

What is already known on this topic?

Long term virological suppression is the surrogate goal of treatment in chronic hepatitis B patients. Lamivudine owns a significant risk of resistance when using long-term. Current experts' guidelines recommend to start chronic hepatitis B treatment with high genetic barrier agents e.g. entecavir, and tenofovir but in many countries, lamivudine is still the first line option due to reimbursement policies. Roadmap concept might improve long term viral suppression outcome in patients who were treated with low genetic barrier agents but real world efficacy data is still limited.

What this study adds?

This is the first proof-of-concept study for application of the roadmap concept to lamivudine therapy in real world practice. At 2 years post treatment, patients in the roadmap group achieved a significantly higher rate of undetectable virus compared with the conventional group. The rates of virological and biochemical breakthrough were also lower in the roadmap group. In developing countries, where low-genetic barrier agents are still the first line option, starting with non-expensive, low-genetic barrier agents, followed by add-on therapy at the proper time according to the roadmap concept, can result in favorable long term treatment outcomes at 2 years.

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Potential conflicts of interest

None.

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