

## Nucleos(t)ide analogues treatment outcome in genotype B and C chronic hepatitis B

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### Abstract

**Background:** Hepatitis B genotypes influence the course and severity of the disease. **Aim:** To compare the treatment outcome of chronic hepatitis B genotype B and C patients after treating with nucleos(t)ide analogues for six months. **Patients and Methods:** Forty chronic hepatitis B patients attending the liver clinic of Hospital for Tropical diseases, Bangkok, were studied in retrospective cohort design. Six genotype B patients (15%) and thirty-four genotype C patients (85%) were treated. Serum hepatitis B viral load, serum alanine amino transferase level, HBeAg status and alpha-feto protein level were measured at the time of starting nucleos(t) analogues therapy, and six months later. Besides, achievement of undetectable viral load was assessed in patients with normal serum alanine amino transferase compared to patients with high serum alanine amino transferase level. **Results:** After six months of nucleos (t) analogues treatment, achievement of undetectable hepatitis B viral load was higher in genotype B patients (66.7%) than in genotype C patients (42.4%) (Relative Risk=1.57, 0.79-3.14). Biochemical remission, HBeAg seroconversion and tumor marker levels between the two groups were not significantly different. Moreover, achievement of undetectable hepatitis B viral load was significantly higher in normal alanine amino transferase level (75%) than in patients with high serum alanine amino transferase level (33.3%) on nucleos(t)ide analogue treatment (Relative Risk=2.25, 1.20- 4.20). **Conclusion:** Chronic hepatitis B treatment outcome between genotype B and C were not significantly different. Patients with normalized serum alanine amino transferase level tend to achieve undetectable viral load after nucleoside analogues treatment.

**Keywords:** Chronic hepatitis B, genotype, treatment, nucleos (t) ide analogues, Thailand.

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### Introduction

Hepatitis B is a disease of global burden and concern. Prevalence of hepatitis B virus (HBV) is extremely high. HBV infects one third of the world population. There are more than 350 million cases of chronic hepatitis B worldwide [1].

HBV infected persons have very high risk for progression to hepatocellular carcinoma (HCC) with relative risk ranging 9.6 to 60.2 [2]. Large cohort studies have shown

association and dose response-relationship of hepatitis B virus DNA (HBV DNA) and HCC carcinogenesis [3, 4]. Infection by HBV genotype C was recognized to be strongly associated with the development of HCC, adjusted relative risk of 10.24 [5].

Currently, there are eight genotypes of hepatitis B virus namely A to H in various regions of the world [6]. In South East Asia, genotype B and C are the major HBV genotypes [7-9]. According to nationwide

sero-epidemiological survey result, majority of CHB in Thailand are genotype C infection (87.1%) and minority are genotype B infection (11.6%) [10].

The goal of treatment in chronic hepatitis B is to reduce the risk of HCC and severe liver disease by lowering HBV replication and limiting the progressive liver damage [11-14]. Currently there are two kinds of treatment for chronic hepatitis B namely interferon therapy and nucleoside analogue (NA) therapy [15]. There is strong evidence that both of these therapies can significantly reduce the risk of HCC [16]. Four NAs such as lamivudine, telbivudine, entecavir, and adefovir have been approved and more widely used in treatment of CHB in Asia [15].

Clinical course and risk of HCC is different between by HBV genotype B and C infection [5]. Studies in Thailand reported the different natural course and severity of CHB between untreated genotype B and C patients [17]. Moreover, genotype B had better response to interferon than genotype C according to previous studies [18-20]. In other word, the interferon therapy cannot change the more severe natural course of genotype C infection. However, response of genotype B and C to widely used NA therapy was reported by a few studies. The results were not conclusive yet across the different ethnic groups of Asian patients [21-23].

It is a matter of interest if NA can change the severe natural course of genotype C HBV infection. Whether the CHB treatment outcome after NA is different between genotypes B and C among Thai patients is not known yet. We aimed to compare the NA treatment outcome between CHB genotype B and genotype C among Thai patients attending Hospital for Tropical Diseases, Bangkok, Thailand.

## Patients and Methods

### *Ethics*

The protocol for this project has been approved by Ethic Committee of the Faculty of Tropical Medicine, Mahidol University, Thailand on 4<sup>th</sup> November 2009 with the certificate of approval (MUTM 2009-047-01).

### *Study population*

Chronic hepatitis B patients who have been attending or attended to hepatitis clinic, Hospital for Tropical Diseases, Bangkok from 2004 to 2009 with the characteristics described in inclusion criteria were retrospectively studied. Forty chronic hepatitis B patients comprising six cases of genotype B and thirty-four cases of genotype C infection were included in the analysis. All were treatment naïve CHB patients received NA therapy for the first time. All were ethnically Thai patients.

### Inclusion criteria

1) Patients diagnosed as chronic hepatitis B by means of HBsAg positivity for more than six months and, presence of HBV-DNA in the serum; 2) HBV-DNA level 5

log<sub>10</sub> copies per /ml or higher in HBeAg positive cases; 3) HBV-DNA level 4 log<sub>10</sub> copies per /ml or higher in HBeAg negative cases; 4) Age between 18 and 70 years; 5) Patients infected with chronic hepatitis B genotype B or C; and 6) Patients receiving any kind of nucleoside analogues therapy for the first time were reviewed, starting from time of getting nucleoside analogue treatment.

### Exclusion criteria

1) Co-infection with HCV (anti-HCV positivity); 2) Co-infection with HIV (evidence of anti-HIV antibody positivity); 3) Chronic hepatitis B patients who had already acquired HCC; and 4) Any patient who had ever received any kind of antiviral treatment for chronic hepatitis B previously were excluded.

The study was carefully designed to have the study population that could answer the research question. The time of inclusion was at the start of NA therapy.

### *Outcome measures*

#### HBV Genotyping

Two methods of HBV genotyping were used. Inno-lipa line probe assay was the method found in most of the cases (80%) and sequence analysis in the rest (20%) of the cases. Sequencing analysis is current gold standard HBV genotyping method and Inno-lipa has been proved as comparable to gold standard [24]. CHB patients with indeterminate or dual genotype results were not included in this study.

#### HBV DNA viral load

Primary outcome of current study is achievement of undetectable HBV-DNA level at sixth month of NA therapy. Undetectable HBV-DNA in current study means HBV-DNA level less than 3 log<sub>10</sub> copies per ml.

Two methods of viral load testing were noted on reviewing the records: COBAS Amplicor Monitor test (3x10<sup>2</sup>-2x10<sup>5</sup> copies per ml) in majority of the test result and Abbott Real time TaqMan HBV (12-110 x10<sup>6</sup> IU/ml, 1 IU= 5.82 copies per ml) in few cases. Despite different level of minimal and maximal detection limit in these two methods, both method can detect HBV-DNA level lower than 3 log<sub>10</sub> copies per ml. Therefore, undetectable viral load in this study could be uniformly considered as less than 3 log<sub>10</sub> copies per ml.

### *Other tests*

Immunological and biochemical tests were done at laboratory of the Hospital for Tropical Diseases, Bangkok. Immunological tests for detection of HBsAg, HBeAg, anti-HBe antibody and serum AFP were done by using Electro- chemiluminescent analyzer. Serum ALT and AST were measured by using Cobas 501 enzymatic analyzer.

Serum HBV-DNA level, serum alanine amino transferase (ALT) level, HBeAg status and alpha-feto protein (AFP) level were measured at the time of starting NA therapy and again at six months of treatment. Mean follow up duration

of viral load was 23.47 weeks in the study population.

### Statistical analysis

Data analysis was done by using SPSS version 11.5. Baseline characteristic data of the genotype B and C was summarized descriptively; categorical data by percentage, continuous data by mean, and standard deviation (SD), or median, maximum and minimum based on normality. The Pearson's chi-square test was used for comparison of baseline categorical data. The Fisher's exact test was applied to compare the primary outcome between genotype B and C. The independent sample T-test was used for comparing means of the two groups and Mann-Whitney U test was applied when the continuous data were not in normal distribution. Statistically, significance was defined as P-value less than 0.05 and relative risk was calculated with 95% confidence interval.

## Results

Base line characteristic of the two-genotype groups were comparable. Genotype C patients have notably higher ALT and AST baseline levels than that of genotype B patients (Table 1).

**Table 1** Baseline characters of CHB patients in genotype B and C groups.

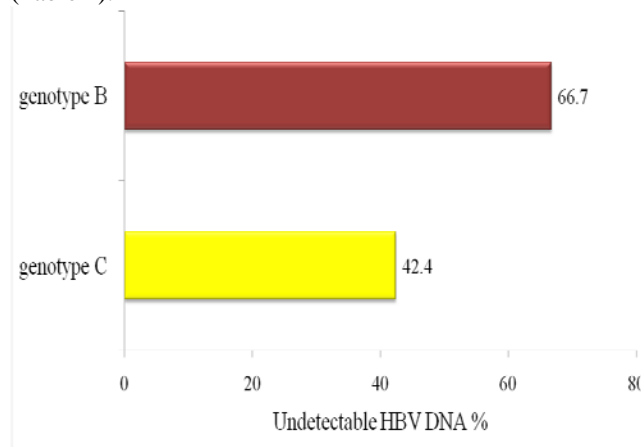
Characteristics	Genotype		P value
	B	C	
Number of patients (%)	6 (15)	34 (85)	
Age (year $\pm$ SD)	40.67 (14.73)	41.46 (11.23)	0.77
Gender (male /female)	3/3	23/11	0.65
Median viral load log <sub>10</sub> copies ( $\pm$ SD)	6.59 ( $\pm$ 1.6)	6.53( $\pm$ 1.16)	0.92
Median ALT IU/L (max-min)	21(98-16)	60 (450-19)	0.88
Median AST IU/L (max -min)	22(66-15)	47(570-22)	0.03
AFP ng/ml ( $\pm$ SD)	2.4 ( $\pm$ 1.33)	4.9( $\pm$ 4.98)	0.17
HBeAg positive CHB no. (%)	5 (83.3)	20 (64.5)	0.64
History of alcohol	0	0	
Cirrhosis by screening USG	0	0	
Nuclos(t)ide analogues treatment			
Lamivudine treated no. (%)	2 (33)	12 (35)	
Telbivudine treated no. (%)	2 (33)	11 (32.3)	
Adefovir treated no. (%)	2 (33)	8 (23.5)	
Entecavir treated no. (%)	0	3 (8.8)	

USG = Abdominal Ultrasound examination

### Virological outcome

After treating with NA for six months, 66.7% of genotype

B infected patients achieved undetectable viral load but 42.7% of genotype C infected patients achieved the undetectable viral load (Fig. 1). Genotype B has higher rate of getting undetectable HBV DNA than genotype C. Relative risk was 1.57 (95% CI 0.79 to 3.14). The difference was not significant statistically ( $P=0.39$ ) (Table 2).



**Fig. 1** Proportion of CHB genotype B and C patients achieved undetectable HBV-DNA viral load at sixth month of NA therapy.

**Table 2** CHB Treatment outcome of Genotype B and C at sixth month of nucleos(t)ide analogue therapy.

CHB treatment outcome	Genotype B (%)	Genotype C (%)	Relative risk (95% CI)	P value
Undetectable HBV-DNA * <sup>?</sup>	66.7	42.4	1.57 (0.79-3.14)	0.39
ALT normalization <sup>\$</sup>	50	29.4	1.7 (0.65-4.42)	0.37
HBeAg status <sup>#</sup>				
HBeAg conversion	0	10		
HBeAg positive	20	10		
antiHBe positive	80	80		
antiHBe negative				
Median AFP level ng/ml <sup>^</sup>	2.67	3.05		0.32

\*n=39, one patient in genotype C group still could not have viral load result at analysis. <sup>?</sup>Undetectable HBV-DNA means HBV DNA less than 3 log<sub>10</sub> copies /ml, <sup>\$</sup> n=40, ALT normal value less than 30 IU/L for male and less than 19 IU/L for female, <sup>#</sup>n= 25, the subset of HBeAg positive CHB patients only, <sup>^</sup>n=38, two of the patients in genotype C group still could not have follow up AFP at sixth month at analysis, CHB: chronic hepatitis B.

### Biochemical outcome

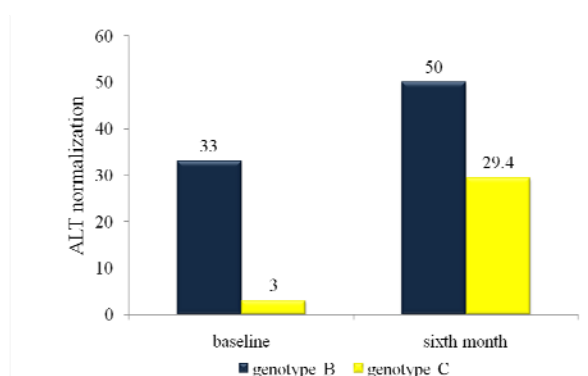
Biochemical remission was compared by normalization of ALT (Fig. 2). After treating with NA for six months, proportion of ALT normalized patients was 50% in genotype B vs. 29.4% in genotype C group (Table 2). Genotype B group has higher proportion of ALT normalization than genotype C group. Relative risk was 1.7 with 95% CI 0.65-4.42. The difference was statistically not significant ( $P=0.37$ ).

### Immunological outcome

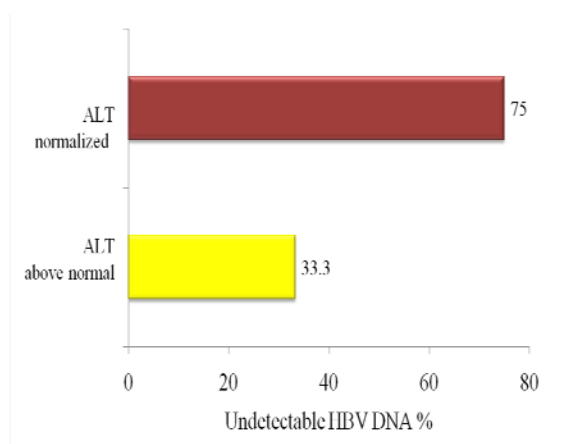
HBeAg seroconversion was defined as disappearance of

HBeAg and appearance of anti-HBe antibody in HBeAg positive chronic hepatitis B patient. After treating with NA for six months, 10% of genotype C infected patients had HBeAg seroconversion whereas no one in genotype B group. Two out of twenty genotype C patients (10%) has attained anti-HBe antibody with the disappearance of HBsAg. Another two genotype C patients (10%) had both anti-HBe antibody and HBeAg at the same moment. One out of five genotype B patients had anti-HBe antibody but HBeAg was still positive. None of the genotype B patients had HBeAg seroconversion at sixth month of NA therapy. Both genotype groups had same proportion 80% with HBeAg positivity and lack of anti-HBe antibody (Table 2).

Median AFP levels were compared between CHB genotype B and C infected patients at sixth month of nucleoside analogue therapy and were not significantly different ( $P=0.32$ ) (Table 2).



**Fig. 2** ALT normalization in CHB genotype B and C at sixth month of NA therapy. (ALT normal value less than 30 IU/L for male and less than 19 IU/L for female was used for analysis).



**Fig. 3** Achievement of undetectable HBV DNA at sixth month post treatment in ALT normalized group and higher than normal ALT groups. (ALT normal value less than 30 IU/L for male and less than 19 IU/L for female was used for analysis.). Relative risk =2.25, 95% CI 1.20 to 4.21 ( $P=0.02$ ).

#### *Correlation of virological outcome and on- treatment ALT normalization*

Undetectable viral load was compared between ALT normalized patients and high ALT patients. Significantly higher proportion of ALT normalized patients had achieved undetectable HBV-DNA on NA treatment (Fig.

3). On-treatment ALT normalization was significantly correlated with achievement of undetectable HBV-DNA at sixth month of NA therapy. Virological response was significantly better in ALT normalized patients than in high ALT patients. Relative risk was 2.25, 95% CI 1.20 to 4.21 ( $P=0.02$ ).

## **Discussion**

Currently, there are two types of therapy for chronic hepatitis B: interferon therapy and NA therapy. NAs are widely used in Asian countries also in Thailand [25]. There are eight known genotypes of hepatitis B (A-H) variably present in different geographical location and ethnicity. Thailand has two common HBV genotypes, B and C. HBV genotype C is predominant in all regions of Thailand accounting for 70% to 97% of the CHB [10].

Previous studies on NA treatment outcome between CHB genotype B and C across various ethnic populations had given the different answers. The comparison results were not yet conclusive. Previous studies in Thailand had revealed that HBV genotype B and C infection had different natural course and severity [17]. However genotype specific-treatment outcome in Thai patients is unknown. Our study result is expected to assist the practicing physicians for prediction of the treatment outcome of NA therapy at sixth month post treatment in the scope of HBV genotypes.

#### *Genotype impact on treatment outcome of CHB*

Current study found out that the proportion of patients achieved undetectable HBV-DNA were not different significantly among genotype B and C after treating with NA for six months. Moreover, the proportion of ALT normalization, HBeAg seroconversion and AFP level were also not significantly different between genotype B and C infection. NA treatment response in term of currently used surrogate outcome markers was not likely to be different between CHB genotype B and C among Thai patients at our hospital setting.

Result of current study is worthwhile to be compared with the context of previous studies. Wiegand and colleagues had reported the combined analysis genotype- specific HBV treatment outcome in exiting evidence [26]. Combined analysis included the published studies of sample size above 30 with different kinds of NA treatment and different outcome measures. Data from three randomized trials and five observational studies were included in their analysis to compare genotype B vs. C and A vs. D HBeAg positive hepatitis. Three studies comprising two trials and one observational study on treatment outcome of lamivudine were included in their analysis for HBeAg negative patients. The finding of that combined analysis revealed that treatment response was not different between genotype B and C. That analysis did not contain Thai ethnicity. Our study result is concurring with result of that combined analysis and adding up the scientific evidence with CHB outcome in Thai ethnicity.

In our study, HBeAg conversion between two genotypes was not significantly different. However, the number in HBeAg positive hepatitis subgroup was small to claim the finding. Time for outcome measure, six months might not be long enough to observe HBeAg conversion in most of the cases. Genotype C group has 10% HBeAg conversion. Genotype B group did not have any case of HBeAg seroconversion meanwhile 20% of the genotype B patients were positive for both HBeAg and anti-HBe antibody. Chan, et al. 2003 had reported that hepatitis B genotypes had no impact on HBeAg seroconversion after lamivudine therapy [21]. Their prospective study in Hong Kong had 35 patients on lamivudine and 96 controls. The author demanded the study in other area and ethnic groups. Current study result in Thai patients is agreeing with result in Hong Kong population.

It was interesting that two clinical trials had reported the different genotype-specific CHB outcome of the same NA in different location and ethnic groups. Zeng and colleagues 2008 had reported the difference in HBV DNA reduction at 48 weeks post-treatment by adefovir therapy between CHB genotype B and C in Chinese Han population [27]. Comparison was by mean of percentage of HBV DNA level reduction to less than 3 log<sub>10</sub> copies per ml. Sample size was 183. It was notable that 24 weeks response was not different between two genotype groups.

On the other hand, Westland, Delaney and colleagues 2003 reported that reduction in HBV DNA after 48 weeks of adefovir dipivoxil 10 mg was not different among genotype B and C [28]. It was a multinational trial of 694 participants at analysis. In that multinational trial, some patients from Thailand were also enrolled to the study [28]. The author raised the question of predominant genotype in each country and relation between genotype and clinical response.

Even bigger study with the same agent of NA revealed negative result in multi-ethnicity despite the positive result in study population entirely composed of Chinese Han population. In the current study, host and pathogen factors were fixed as Thai ethnicity and HBV genotype B and C. Therefore, the context of current study is of the same opinion with suggestion of previous prospective randomized controlled trials.

It is likely that the treatment response of genotype B and C are not different after NA therapy despite the different natural history of two genotypes, B and C. The result of current study can be applied only up to six-month post treatment. In future research, long-term treatment outcome should be explored.

#### *On- treatment ALT normalization and undetectable HBV-DNA*

Moreover, it was found that NA treated patients with normal ALT at sixth month of therapy had achieved undetectable HBV-DNA significantly higher than patients with high ALT. In case of interferon therapy, high ALT is a

predictor of good virological response [13]. Current study finding would be a distinct feature of NA treated CHB patients in both genotype B and C infection. On NA treatment, ALT normalized patients are two to four times more likely to get undetectable viral load than patients with ALT level higher than normal.

It would be a useful application to predict the early virological response in the practice of CHB, in resource limited setting especially in Asia.

## Conclusion

Up to sixth month of NA therapy, CHB treatment outcome is not different between genotype B and C. ALT normalized patients have better virological outcome on NA treatment.

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## Author Contributions

Aung MN and Leowattana W designed the study. Leowattana W, Tangpukdee N and Kittittrakul C edited the research proposal developed by Aung MN. Aung MN collected the clinical data with the guidance of Leowattana W. Aung MN performed the data analysis and interpretation planned by Tangpukdee N. Aung MN wrote the manuscript which was finally edited by Leowattana W, Tangpukdee N and Kittittrakul C.

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