Original Article

Observation of genotype C infected chronic hepatitis B patients in clinical practice

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Abstract

Introduction: Hepatitis B virus (HBV) genotype C is prevalent in many areas of the world including Thailand and Southeast Asia. It is a strong risk for hepatocellular carcinoma (HCC) by evidence. We aimed to describe the baseline clinical information of treatment naïve genotype C infected chronic hepatitis B (CHB) patients and to describe the treatment response by surrogate outcome markers in genotype C infected CHB patients after one year of nucleos(t)ide analogues (NA) treatment

Methodology: Thirty-four genotype C CHB patients were studied at the Hospital for Tropical Diseases, Bangkok, including 12 patients treated with lamivudine, 11 with telbivudine, 8 with adefovir, and 3 with entecavir. Serum HBV DNA levels, serum alanine amino transferase (ALT) levels, HBeAg status, and alpha-feto protein (AFP) levels were recorded at the start and after twelve months of ongoing treatment. HBV genotyping was performed by line-probe assay.

Results: About half of the patients (58.8%) were HBeAg positive. Mean HBV viral load was 6.53 $\pm$ 1.15 $\log_{10}$ copies per ml at baseline and reduced to 3.63 $\pm$ 1.3 $\log_{10}$ copies per ml after one year of NA treatment. Serum HBV DNA levels became undetectable in 47.1 % of the patients and serum ALT was normalized in 23.5 % of the patients.

Conclusion: Most of the genotype C patients were aged above 40 years. More than half of the genotype C infected patients did not achieve virological response and biochemical remission. Among the CHB patients, genotype C infected patients are a high priority group for intervention.

Key words: Genotype C hepatitis B; chronic hepatitis B; Thailand

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Introduction

Hepatitis B is a disease of global burden infecting one third of the world population. There are more than 350 million cases of chronic hepatitis B (CHB) worldwide [1]. Chronic HBV infection is the most prevalent cause of hepatocellular carcinoma accounting for 55% of global cases and 89% of those in HBV endemic regions [2]. Among CHB patients, genotype C infected patients are a high-risk group for severe chronic liver disease and hepatocellular carcinoma [3,4].

HBV infected persons have a very high risk for progression to hepatocellular carcinoma (HCC) with relative risk ranging from 9.6 to 60.2 depending on HBe antigen positivity [5]. Existing evidence has shown two strong risk factors for HBV related hepatocellular carcinoma: serum hepatitis B virus DNA level and genotype C virus [4,6,7]. Worldwide cohort studies have described the increasing risk of HCC with higher levels of serum hepatitis B virus DNA [6,7]. Infection by HBV genotype C was conclusively recognized to be strongly associated with the development of HCC, adjusted relative risk of 10.24 [4].

Eight CHB genotypes have been known, namely A to H, in various regions of the world whereas genotype C is prevalent in Southeast Asia, China, Korea, Hong Kong, Japan, Australian aborigines and the Solomon Basin, Hawaii and North America [8]. According to nationwide sero-epidemiological survey results, HBV genotype C infection is extremely prevalent in Thailand (87.1%) [9]. In the four major regions of Thailand, genotype C prevalence was 82% in the northern part, 70% in the central region, 95% in the southern part and 98% in the north-eastern part[9]. Moreover, among the CHB patients who are migrant workers from neighboring countries such as Myanmar, Cambodia and Laos, genotype C

infection is predominant accounting for 86% of patients [10]. In the hospital based setting, genotype C infected patients may even account for a higher proportion of CHB patients. Such a high prevalence of genotype C HBV can lead to high incidence of liver cancer among CHB patients in Thailand and its neighboring regions; thus attention from public health officials and early interventions are needed.

Two kinds of treatment are currently used for chronic hepatitis B, namely interferon therapy and nucleos(t)ide analogue (NA) therapy [11]. Genotype C CHB is clinically more severe than infection from the other genotypes [12]. Clinical studies in different regions reported that interferon therapy was less effective for genotype C CHB [13-15]. At present, NAs such as lamivudine, telbivudine, adefovir, entecavir and tenofovir have become major treatment options for genotype C and are widely used around the world [11,16]. A study revealing the patterns of treatment response to these drugs among the extremely prevalent genotype C CHB infection is still lacking and worthwhile to undertake.

Therefore, we aimed to describe the features of the high-risk genotype C infected patients at initial presentation to our liver clinic. We aimed to describe features of genotype C infected CHB patients after one year of treatment with nucleos(t)ide analogues.

Methodology

Ethics

This study was approved by the ethics committee of the Bangkok School of Tropical Medicine, Mahidol University, Thailand, on 4 November 2009(certificate of approval MUTM 2009-047-01).

Study population

A total of 34 genotype C chronic hepatitis B patients were included in the study. Treatment naïve CHB patients receiving NA as the first time treatment were carefully selected based on inclusion and exclusion criteria. All were ethnically Thai patients who had been attending or attended to the hepatitis clinic, Hospital for Tropical Diseases, Bangkok, from 2004 to 2009. All CHB patients met the following criteria.

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 $\log_{10}$ copies per /ml or higher in HBeAg positive cases
3. HBV-DNA level 4 $\log_{10}$ copies per /ml or higher in HBeAg negative cases
4. Age between 18 and 70 years
5. Patients infected with chronic hepatitis B genotype C
6. Naïve patients receiving any NA for the first time

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 at presentation
4. Treatment with other antiviral therapy than nucleos(t)ide analogues

Serum AFP and abdominal ultrasound examination were used to screen the HCC at presentation. The time of inclusion was at the start of NA therapy. Only the regularly followed up patients were included in the analysis.

Study design

This investigation was a longitudinal observational study. Clinical data were collected retrospectively.

Outcome measures

HBV Genotyping: Line probe assay HBV genotyping, (Inno-Lipa, Innogenetics NV, Gent, Belgium) was used. Sequence analyses comprise the gold standard HBV genotyping method and Inno-lipa has already been proven as comparable to the gold standard in existing literature [17]. CHB patients with indeterminate or dual genotype results were not included in this study.

HBV DNA viral load: Undetectable HBV-DNA in the current study means HBV-DNA levels were less than 3 $\log_{10}$ copies per ml (cp/ml). Two methods of quantitative HBV DNA viral load measurement were applied: COBAS Amplicor Monitor assay (Roche Diagnostics, Basel, Switzerland), range of detection of $3x10^2$-$2x10^5$ copies per ml (in the majority of the cases) and Abbott Real Time HBV assay (Abbott Laboratories, Abbott Park, IL, USA), range of detection of 10-110 $x10^6$ IU/ml,(1 IU = 3.41 copies/ml) in a few cases. Both methods can detect HBV-DNA levels less than 3 $\log_{10}$ copies per ml. Undetectable viral load in this study therefore could be uniformly considered as less than 3 $\log_{10}$ copies per ml.

Table 1. Characteristics of CHB in genotype C treatment naïve patients at the time of diagnosis

Characteristics genotype C CHB at Diagnosis	**Number (%)**
Number of patients	34
Ethnicity	
Thai	34 (100)
Age	
Mean age (year ± SD)	41.46 (11.23)
Above 40	24 (70.6)
Younger than 40	10 (29.4)
Sex	
Male	23 (67.6)
Female	11 (32.4)
Risk factors	
Duration of exposure not known	29 (85)
Family history of hepatitis B	3 (17)
Blood transfusion history	1 (2.9)
Health care workers	1 (2.9)
Base line laboratory parameters	
Mean viral load log $_{10}$ copies (± SD)	6.53 (± 1.15)
Median ALT IU/L (max-min)	60 (450-19)
Median AST IU/L (max -min)	47 (570-22)
AFP ng/ml (± SD)	4.9 (± 2.98)
HBe Ag positive CHB	20 (58.8)
Nucleos(t)ide analogues treatment	
Lamivudine	12 (35.3)
Telbivudine	11 (32.3)
Adefovir	8 (23.5)
Entecavir	3 (8.8)

N (%) shows number and percentage unless specified otherwise ALT: alanine aminotransferase, AST : aspartate aminotransferase
AFP: alpha feto-protein, CHB: chronic hepatitis B

Other tests: Biochemical and immunological tests were performed at the clinical laboratory of the Hospital for Tropical Diseases, Bangkok. Immunological tests for detection of HBsAg, HBeAg, anti-HBe antibody and serum alpha feto protein (AFP) were conducted by using an Elecsys 2010 analyzer (Roche Diagnostics, Basel, Switzerland). Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured by using the Cobas c501 analyzer (Roche Diagnostics, Basel, Switzerland). These markers were checked on the average of every three months at the study site hospital.

ALT normalization

ALT normal values were based on 2008 US Panel recommendations [26]. Serum ALT levels less than 30 IU/L for males and less than 19 IU/L for females were considered as ALT normalization.

Statistical analysis

Data analysis was performed using SPSS version 11.5 (IBM, Chicago, IL, USA). Baseline characteristic data of the study cohort were summarized descriptively. Categorical data are summarized by percentage, continuous data by mean, and standard deviation (SD), or median, maximum and minimum based on normality. Surrogate markers of treatment response were compared between baseline levels and twelve months after treatment. Paired sample t test or Wilcoxon signed-rank test were used to compare the levels of surrogate markers depending on the distribution of quantitative data. Fisher's exact test was used for comparing categorical

Table 2. Surrogate markers at twelve month after receiving drug (nucleos(t)ide analogues)

Surrogate markers of genotype C CHB* treatment outcome	Baseline	Treatment outcome at one year	P-value
Mean viral load log $_{10}$ copies (±SD)	6.53 (±1.15)	3.63 (± 1.3)	< 0.001
Median ALT IU/L (min-max)	60 (19-450)	36 (15-121)	< 0.001
Median AST IU/L (min-max)	47 (22-570)	32 (16-85)	< 0.001
AFP ng/ml (±SD)	4.9 (± 2.98)	3.14 (1.5-13.6)	0.227
HBeAg positive CHB	20 (58.8)	18 (52.9)	< 0.001

*CHB: Chronic hepatitis B

data. Statistically, significance was defined as a P-value less than 0.05.

Results

Baseline characters of treatment naïve genotype C CHB

Clinical characteristics of the treatment naïve CHB patients infected with genotype C in the study are shown in Table 1. All the patients were ethnically Thai patients with a mean age of 41.46 years. Most of the patients were above the age of 40 years. The number of male patients was higher than that of female patients. Seventeen percent of the patients revealed a family history of chronic hepatitis B. Eighty-five percent of the patients did not notice being HBV infected before presentation to our clinic and they had not consulted for CHB treatment previously.

Pre-treatment levels of surrogate markers noted at the time of diagnosis are shown in Table 1. Among the studied group, 12 patients received lamivudive (35%), 11 patients received telbivudine (32.3%), 8 patients received adefovir (23.5%), and 3 patients received entecavir (8.8%).

Treatment response in genotype C CHB after one year of NA treatment

Changes in the surrogate markers were assessed at diagnosis and at one year follow-up after treatment as shown in Table 2.Overall, levels of the markers were improved quantitatively one year after treatment. Median viral load was reduced from 6.53log$_{10}$ copies per ml to 3.63log$_{10}$ copies per ml. (p-value 0.001). Median serum ALT level was reduced from 60 IU/L to 36 IU/ml. (p-value 0.001). Median serum AST level was reduced from 47 IU/l to 32 IU/L (p-value 0.001). Mean serum AFP level was also reduced after treatment but not significantly statistically.

We also checked the proportion of patients who achieved virological outcome, biochemical remission and HBeAg seroconversion after one year of NA therapy. As shown in Table 3, serum HBV DNA levels became undetectable (less than 3 log copies /ml) in 47.1% of the patients. Serum ALT levels were normalized in 23.5% of the patients. Tumor marker AFP levels were normal in 79.4% of the patients. HBeAg loss with appearance of anti-HBe antibody occurred in 10% of the HBeAg positive patients.

Treatment outcomes were further compared among patients who received various nucleos(t)ide analogues by analyzing average baseline levels of surrogate markers and after twelve months of ongoing treatment (Table 4). These results were meant to describe the host-virus interaction on one year NA treatment.

All the CHB patients were followed up every six months to check serum AFP levels and yearly for abdominal ultrasound. Out of 34 cases, five had abnormally high serum AFP levels at six months after commencing NA treatment. Out of those five cases, two cases of hepatocellular carcinoma (HCC) were detected at one-year and three-year follow-ups respectively and confirmed by computed tomography (CT) scan. The two CHB cases at the time of diagnosis for HCC had undetectable HBV DNA viral loads and normal ALT levels. Serial follow-ups showed progressively high levels of serum AFP in two HCC cases (Figure 1).

Discussion

It is important to know the treatment response of prevalent HBV genotypes to widely used treatments in a region, preferably in a particular ethnic group [18]. A current investigation composed of only genotype C infected, Thai, CHB patients who were all on NA treatment may provide valuable information about the genotype-specific anti-viral effectiveness in a hepatitis B endemic setting. Our study objective was to show the overall treatment outcome picture of genotype C infected patients treated by nucleos(t)ide analogues descriptively.

In previous studies, clinical trials on NA did not report the treatment endpoint by HBV genotypes [18]. Treatment responses were usually reported by a decrease in HBV DNA levels quantitatively [27].

Figure 1. Base line and follow up of genotype C CHB patients with high serum AFP on NA treatment

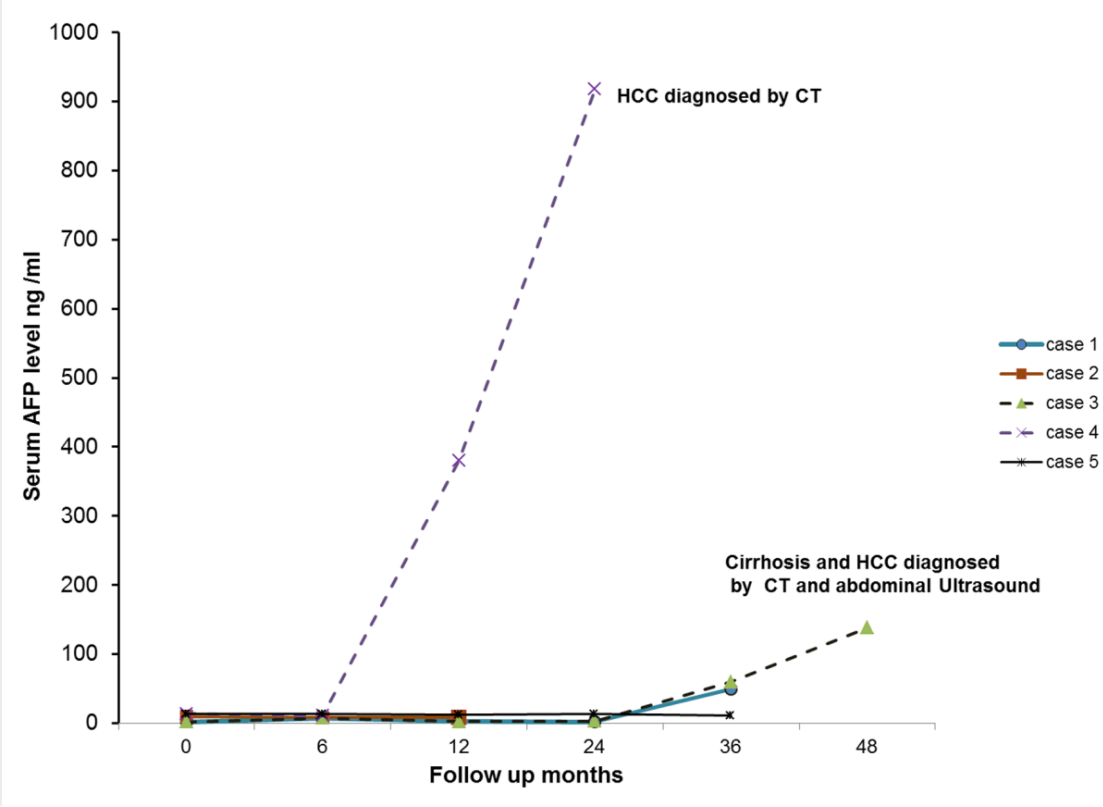

Table 3. Proportion of treatment outcome in genotype C chronic hepatitis B patients after one year of nucleoside analogues treatment

Treatment outcome of genotype C CHB at one year [n]	**Achievement n (%)**
Undetectable viral load[*]	16 (47.1)
ALT normalization [#]	8 (23.5)
AFP normal level [+]	27 (79.4)
HBeAg seroconversion [^]	2 (10.0)

[n] n = 34. * Undetectable viral load less than 3 $\log_{10}$ copies per ml [#] ALT normal value less than 19IU/L for female less than 30 IU/L for male was used for this analysis [+] Normal AFP level less than 7 ng /ml [^] HBeAg seroconversion means loss of HBeAg and appearance of anti-HBe antibody in HBeAg positive hepatitis CHB: chronic hepatitis B

However, categorical analysis by proportion of outcome achievement may lead to a different conclusion. In our study, after one year of NA treatment, HBV DNA levels were undetectable in less than half (47.1%) of the patients. Less than one fourth of the patients (23.5 %) achieved ALT normalization. Ten percent of the HBeAg positive patients showed HBeAg seroconversion. Descriptively, the proportions of treatment response achievement were poor (Table 3), despite the quantitative improvement of surrogate marker levels (Table 2). It could be explainable as a more severe kind of genotype C HBV infection. Similarly, Zeng and colleagues [20] reported 34.6% undetectable HBV DNA attainment after 48 weeks of adefovir therapy in genotype C infected Chinese Han CHB patients.

HBV genotype C, which is a high risk for liver cancer, is predominant in all regions of Thailand [9]. Genotype C infected CHB patients in this study had mean ages above 41 and more than 70% of the patients were over forty years of age. It is notable that the mean age of the current study population was older than the mean ages of CHB patients in other

Table 4. Levels of HBV DNA and ALT at base line and after twelve months of therapy

	Average HBV-DNA (log_{10} copies/ml) mean (min-max)		**Average ALT (IU/ml) median (min-max)**		**HBeAg positive hepatitis n (%)**	
Treatment	base line	after 12 months	base line	after 12 months	base line	after 12 months
lamivudine	6.77	3.63	60	30	6	6
n = 12	4.75-7.6	3-5.11	26-296	13-199	(50)	(50)
telbivudine	6.61	3.56	52	30	8	7
n = 11	4.82-8.04	1.08-8.04	19-450	23-42	(72.7)	(63.6)
adefovir	5.73	3.38	85	28	4	3
n = 8	4.14-7.14	1.74-5.16	31-282	13-53	(50)	(37.5)
entecavir	7.40	4.56	51	36	2	2
n = 3	6.53-8.08	3.67-5.55	38-111	21-56	(66.7)	(66.7)
all patients	6.53	3.63	60	36	20	18
n = 34	4.14-8.08	1.08-8.04	(19-450)	(15-121)	(58.8)	(52.9)

Average values are shown in mean (min-max) for normally distributed data and median (min-max) for data not in normal distribution. Max means maximum. Min means minimum.

Asian studies (33.1 years in China, 34.9 years in Taiwan 34.9, and 29 years in Hong Kong) [4,19,20].

According to epidemiological patterns, HBV transmission usually occurs at an earlier age of life in an endemic area such as Thailand [1,21]. Most of the patients (85%) in the current study were not aware of the possible time they had acquired Hepatitis B the infection (Table 1). Older age at presentation and not knowing the duration of exposure jointly suggests late presentation of CHB patients at the study site hospital. The course of hepatitis B after the fourth decade of life is more severe and associated with a higher chance of cirrhosis and cancer [22]. Therefore, community awareness should be raised about the treatment of CHB to prevent liver cancer.

The current goal of treatment in chronic hepatitis B is to reduce the risk of HCC and severe liver disease by lowering HBV replication and limiting progressive liver damage [23-26]. Incidence of HCC among a population who received treatment has not yet been described in the literature. Meta-analysis results showed that both interferon and NA therapies can reduce the risk of HCC [28]. A sustained undetectable HBV DNA level is the current surrogate treatment outcome and achievement of that may prevent the progression to cancer [23-26]. In our study cohort of genotype C infected CHB patients, the overall treatment response of the patients was not satisfactory, as were reported CHB outcomes in the literature [23-26]. We have observed two cases of HCC among patients with high serum AFP levels on NA treatment. Both cases had attained undetectable viral load and ALT normalization before the flare up of AFP and detection of HCC (data not shown). It is questionable whether HBV genotype C has a high-risk tendency for carcinoma despite undetectable HBV DNA levels. Our sample size was not big enough to reflect such incidence of HCC; therefore, we recommend future prospective studies composed of a high-risk genotype C infected CHB population with long-term follow-up on NA treatment.

Study limitations

The current study had limitations as it was assembled in a narrow time frame with limited resources. However, these data were collected at a tertiary hospital setting in a developing country. HBV genotyping is not a routine test performed for CHB patients in our setting. It was very difficult to acquire the genotype data and serial follow-up of surrogate markers. During the study period, there was a small number of patients who received entecavir because of the higher cost of second-generation nucleos(t)ide analogues. Our finding of treatment outcomes among genotype C CHB patients was an attempt to generate a hypothesis rather than prove a hypothesis.

Conclusion

More than half of the genotype C chronic hepatitis B patients did not achieve virological clearance and biochemical remission after one year of treatment with nucleos(t)ide analogues. Genotype C infected patients are high-priority group for intervention. Hospital based clinical information and treatment outcome descriptions of such a high-risk population would be useful for current practice, future studies and public health awareness. Our study results are expected to relay important information

about the high-risk population among CHB patients in Thailand, its neighboring countries and globally.

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