An Observational Study to Evaluate the Safety and Efficacy of Telbivudine in Adults with Chronic Hepatitis B

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ABSTRAK

Tujuan: *untuk menilai keamanan dan efektifitas terapi telbivudine pada pasien dewasa dengan CHB di Indonesia.* ***Metode:*** *desain penelitian adalah kohort prospektif. Penelitian multisenter pada pasien CHB dewasa yang memerlukan terapi antiviral oral dalam praktik klinis sehari-hari. Seluruh pasien menerima 600 mg telbivudine setiap hari selama satu tahun. Rekrutmen dan keputusan untuk memulai terapi telbivudine didasarkan pada indikasi klinis yang dinilai oleh dokter yang berpartisipasi. Diutamakan adalah keselamatan pasien (adverse event atau efek samping yang serius), sedangkan titik akhir sekunder adalah serokonversi HBeAg, perubahan serum tingkat DNA HBV dan serum ALT normalisasi. Pasien dinilai pada minggu ke-24 dan ke-52 setelah terapi.* ***Hasil:*** *sebanyak 176 kasus yang memenuhi kriteria untuk dianalisis, 104 (59,8%) HBeAg-positif dan 70 (40,2%) pasien HBeAg-negatif. Efek samping yang dilaporkan pada 7 (4,0%) pasien, kebanyakan dari mereka adalah ringan. Hilangnya HBeAg dan tingkat serokonversi sebesar 28,8% dan 14,14%, masing-masing pada minggu ke-52. Tidak terdeteksi HBV DNA (PCR negatif) 51,8% pada minggu ke-24 dan 62,7% pada minggu ke-52. Median tingkat HBV DNA secara signifikan berkurang dari awal sampai minggu ke-24 dan minggu ke-52 setelah terapi (p<0,001, uji Wilcoxon signed-rank). Normalisasi aktivitas ALT serum terjadi pada 85 (73,28%) pasien pada minggu ke-52.* ***Kesimpulan:*** *terapi Telbivudine umumnya aman dan dapat ditoleransi dengan baik pada pasien Indonesia dewasa dengan hepatitis B kronis. Pada pengobatan hilangnya HBeAg serokonversi, perubahan tingkat HBV DNA, dan normalisasi ALT serum ditemukan hasil yang sama dengan studi sebelumnya.*

Kata kunci: *Alanine aminotransferase, hepatitis B kronis, HBV DNA, pengobatan antivirus oral, terapi telbivudine.*

ABSTRACT

Aim: *to assess the safety and efficacy of telbivudine therapy in adult patients with CHB in Indonesia.* ***Methods:*** *the study design was prospective cohort study. Multicenter study of adult CHB patients requiring oral antiviral therapy in daily practice setting. All patients received 600 mg of telbivudine daily for one year. Recruitment and decision to start telbivudine therapy was based on clinical indication as assessed by the participating physicians. The primary end-point was patient safety (adverse event or serious adverse events); while the secondary end-points were HBeAg seroconversion, changes of serum HBV DNA levels and serum ALT normalization. Patients were assessed at week-24 and week-52 of treatment.* ***Results:*** *a total of 176 cases were eligible for analysis, comprising 104 (59.8%) HBeAg-positive and 70 (40.2%) HBeAg-negative patients. Adverse events were reported*

in 7 (4.0%) patients, most of them were mild. HBeAg loss and seroconversion rate was 28.8% and 14.14% at week-52 respectively. Undetectable HBV DNA (PCR negativity) was 51.8% at week-24 and 62.7% at week-52. Median HBV DNA levels were significantly reduced from baseline to week-24 and week-52 treatment (both p<0.001; Wilcoxon's signed-rank test). Normalization of serum ALT activity occurred in 85 (73.28%) patients at week-52. ***Conclusion:*** *Telbivudine therapy is generally safe and well tolerated among adult Indonesian patients with chronic hepatitis B. Treatment efficacy in terms of HBeAg loss and seroconversion, changes of HBV DNA levels and serum ALT normalization were similar to previous reported studies.*

Key words: *Alanine aminotransferase, chronic hepatitis B, HBV DNA, oral antiviral treatment, telbivudine therapy.*

INTRODUCTION

Chronic hepatitis B (CHB) is still a major public health problem in Indonesia. Persistence of active hepatitis B virus (HBV) infection is associated with morbidity and mortality in CHB due to the progression to cirrhosis or hepatocellular carcinoma.[1,2] Based on the Asia Pacific Association for the Study of the Liver (APASL) guidelines,antiviral treatment is indicated for CHB patients with serum alanine aminotransferase (ALT) activity more than twice the upper limit of normal (>2x ULN) and HBV DNA levels ≥105in HBeAg-positive or $\geq 10^4$ copies/mL in HBeAg-negative patients.[3]

The long-term goal of CHB treatment is to prevent disease progression to cirrhosis, HCC and death caused by HBV replication and liver inflammation.[4] Unfortunately, complete eradication of HBV infection is impossible due to the persistence of covalently closed circular DNA (cccDNA) in the hepatocytes nuclei.[5,6] Therefore, the main aims of treatment are to achieve HBeAg seroconversion or undetectable HBV DNA levels or both; stop or reduce hepatic necroinflammation; and prevent hepatic decompensation.

Telbivudine demonstrated potent activity against hepatitis B with a significantly higher rate of response and superior viral suppression compared with lamivudine, the standard treatment.[7,8] Telbivudine has been introduced in Indonesia since 2006 but has not been studied in Indonesian population. This study design is aligned with the roadmap concept to optimize therapy in CHB patients.[9] Central to this concept is the use of on-treatment monitoring strategies of early virologic responses which may be predictive of improved outcomes, including reduced risk of anti-viral resistance. This study is primarily designed to assess the safety and efficacy of telbivudine therapy in adult patients with compensated CHB in Indonesia.

METHODS

This was an observational, prospective cohort, multicenter study of CHB patients treated with telbivudine.and was funded by Novartis pharma. Study was conducted on 184 patients from 191 physicians in 7 cities in Indonesia from April 2009 to November 2011.

Inclusion criteria were male or female adult patients, aged more than 18 years, diagnosed with CHB by positive HBsAg for at least 6 months, had HBeAg-positive or -negative, had a clinical history compatible with CHB, and no prior history of CHB treatment. Patients were excluded if there was a known hypersensitivity to telbivudine or any of its ingredients, was pregnant or intended to become pregnant or planned to breastfeed during the study period, or had any clinically significant concurrent severe or unstable medical conditions. Ethical approval was obtained from the Ethical Committee of Medical Research, Faculty of Medicine, University of Indonesia.

Data Collection

Data were collected and recorded in a written case report form (CRF) specifically designed for this study. Assessments and evaluations were performed according to the physician's routine practice and standard care. Data included patient demographics, background characteristics, details of the hepatitis B related medical history,

concomitant diseases, vital signs, laboratory values, adverse events, compliance, and a final physicians assessment of the therapy with regard to effectiveness, safety, and tolerability.

Clinical and Laboratory Assessment

Patients were expected to complete a follow-up period of 52 weeks, including treatment response evaluation at week-24 and week-52. Assessment included safety profile, including the number and type of adverse events (AEs) or serious AEs; virological response (HBeAg loss and seroconversion; serum HBV DNA level changes; PCR negativity (<300 copies/ mL or 60 IU/mL); and normalization of serum ALT enzyme activity (<1x ULN).

Statistical Analysis

Data from the CRF were entered into an electronic database in the Clinical Study Unit, Faculty of Medicine, University of Indonesia. Patients' demographic and baseline data were presented descriptively as percentage for categorical data or mean and standard deviation (SD) for numerical data. Due to well-recognized clinical differences of HBeAg-positive and HBeAg-negative CHB patients,[10,11] analyses were done separately for both groups. Adverse and serious adverse event data were presented and analyzed descriptively. HBeAg loss, HBeAg seroconversion, PCR negativity, and serum ALT normalization were also presented and analyzed descriptively. Median serum HBV DNA changes were analyzed using the Wilcoxon's signed-rank test for skewed data. A p value less than 0.05 was considered significant. Statistical analysis was done using SPSS version 17.0 for Windows PC (SPSS Inc., Chicago, Illinois).

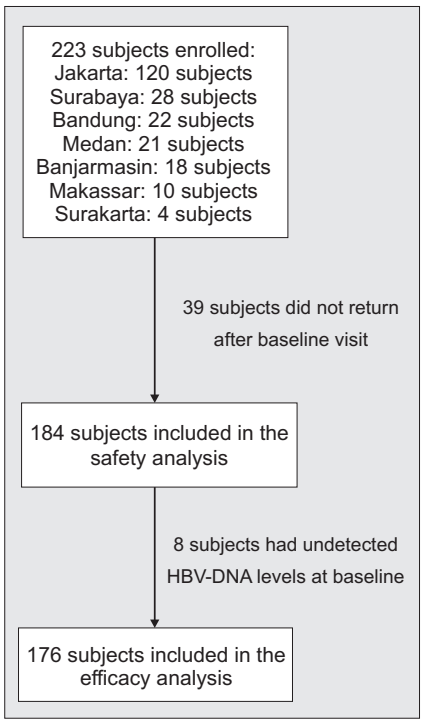

Figure 1. Flow of subjects throughout the study

RESULTS

Characteristics of the Study Subjects

Two hundred and twenty three patients were recruited for this study; 39 patients did not return after baseline visit, resulting with 184 patients to be evaluated for safety analyses. Eight patients had undetected HBV-DNA levels at baseline and were excluded (**Figure 1**). The final number of patients available for efficacy analyses was 176 patients, comprising 106 (60.2%) men and 70 (39.8%) women. Patients mean age was 41.5 years, ranging from 18-70 years old; the basic characteristic of the 176 patients are shown in **Table 1**.

Safety Analysis

The adverse events were reported in 7 (3.8%) patients, most of them were mild. Adverse events were abdominal discomfort (2), neuropathy (1), common cold (1), nausea (1), myotoxicity (1), death (1), and pregnancy (1). The latter was reported by a patient who had a musculoskeletal problem, i.e. spondyloarthritis, and was not related to telbivudine therapy.

Telbivudine treatment was discontinued in one patient because of unexpected pregnancy. Later she gave birth to a healthy baby boy.

Efficacy Analysis

Evaluation of treatment response was done at week-24 and week-52 for all patients receiving treatment. Among HBeAg-positive patients, 9.18% patients achieved HBeAg loss at week 24 and 23.23% at week 52; while seroconversion was detected in 5.10% at week-24 and 14.14% at week-52 (**Figure 2**).

Seventy-two out of 139 patients (51.8%) had undetectable HBV DNA levels (PCR

Table 1. Baseline characteristics of the study subjects (n=176)

Characteristic	All patients* (n=176)	HBeAg (+) (n=104)	HBeAg (-) (n=70)
Gender, n (%)			
- Male	106 (60.2)	61 (58.7)	43 (61.4)
- Female	70 (39.8)	43 (41.3)	27 (38.6)
Age, mean (SD)	41.5 (12.37)	37.9 (12.11)	46.8 (11.01)
- <40 years, n (%)	79 (44.9)	61 (58.7)	17 (24.3)
- >40 years, n (%)	93 (52.8)	41 (39.4)	51 (72.9)
AST level (U/L), mean (SD)	99.8 (159.06)	90.0 (126.68)	115.6 (197.97)
ALT level (U/L), mean (SD)**	114.9 (169.58)	119.1 (192.71)	110.4 (133.66)
- <2x ULN, n (%)	108 (61.4)	61 (58.7)	45 (64.3)
- 2-5x ULN, n (%)	41 (23.3)	28 (26.9)	13 (18.6)
- >5x ULN, n (%)	23 (13.1)	11 (10.6)	12 (7.1)
Albumin (g/dL), mean (SD)	4.2 (0.61)	4.2 (0.58)	4.1 (0.64)
Bilirubin (mg/dL), mean (SD)	1.4 (1.77)	1.2 (1.68)	1.7 (1.86)
HBV DNA (copies/mL)			
- Median	7.45×10^5	9.5×10^5	8.2×10^4
- Range	$107 - 2.6 \times 10^9$	107×10^4-2.6×10^9	$462 - 6.9 \times 10^8$

* 2 patients have missing HBeAg data, thus total patients is 176 while HBeAg(+) plus HBeAg (-) is 174.
** Normal limit was 50 U/L for men and 34 U/L for women

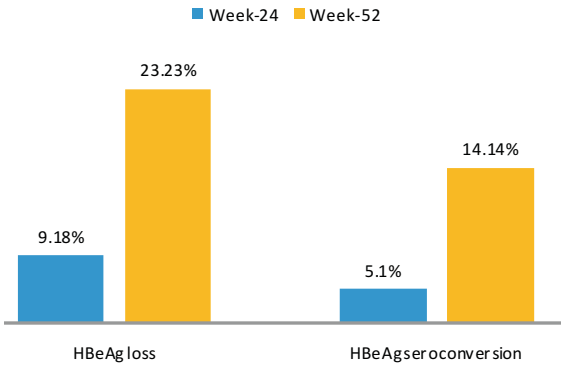

Figure 2. HBeAg loss and seroconversion after treatment

negativity) after 24 weeks of treatment and increased to 62.5% after 52 weeks of treatment. PCR negativity was more profound in HBeAg negative-patients (**Table 2**). In both HBeAg positive and negative patients, there was a significant reduction of median HBV DNA level from baseline at week-24 and week-52 of treatment (**Table 2**). There were 170 patients provided with serum ALT level at week-52. Normalization of serum ALT activity occurred in 73.28% patients (**Table 2**).

DISCUSSION

Our study is the largest prospective, observational study of CHB patients receiving telbivudine done in Indonesia. More male patients participated in this study, which was also reported in many clinical trials,[12-14] including GLOBE trial.[15] For the global prevalence of HBV infection between male and female is almost similar, 3.9% in men and 3.5% in women. However, the prevalence is higher in Southeast Asia (5% to over 6%).[16] HBeAg-negative patients were older than HBeAg-positive patients which was consistent with the natural history ofchronic HBV infection.[17]

From our study, telbivudine therapy was generally safe and well tolerated, which was similar to GLOBE Studies. Adverse events were reported in 7/184 (3.8%) patients, most of them were mild. Types of adverse events were abdominal discomfort (2), neuropathy (1), common cold (1), nausea (1), myotoxicity (1), death (1), and pregnancy (1). Since the AEs were reported by patients during each visit, and occurred shortly before visit, they were estimated unlikely to be related to telbivudine.

Table 2. Treatment response at week-24 and week-52 (n=176)

Treatment endpoint	HBeAg-positive (n=102)		HBeAg-negative (n=70)	
	Week 24	Week 52	Week 24	Week 52
HBV DNA levels (copies/mL)				
Median	1.23 x 10^3	150	Undetected	Undetected
Range	Undetected-1.1x10^8	Undetected-1.1x10^8	Undetected-3.8x10^4	Undetected-1.1x10^8
p from baseline*	<0.001	<0.001	<0.001	<0.001
HBV DNA status by PCR				
- Positive	56 (71.8%)	50 (56.2%)	10 (16.9%)	6 (9.8%)
- Undetected	22 (28.2%)	39 (43.8%)	49 (83.1%)	55 (90.2%)
Total	78 (100.0%)	89 (100%)	59 (100%)	61 (100%)
p between visit 3 & 4		0.000		0.000
Serum ALT status				
- Above ULN	34 (34.7%)	26 (26.3%)	14 (20.3%)	10 (14.5%)
- <1x ULN	64 (65.3%)	73 (73.7%)	55 (79.7%)	59 (85.5%)
Total	98 (100%)	99 (100%)	69 (100%)	69 (100%)
p between visit 3 & 4		0.000		0.000

*Wilcoxon's signed-rank test

For myotoxicity, the patient had specific musculoskeletal abnormality in the form of spondyloarthritis which probably caused this AE. This abnormality could lead to instability and fall. Thus, the presence of myotoxicity in this case as well as its relationship with telbivudine is questionable.

Other studies have shown the incidence of myopathy, characterized by myalgia and increase in creatine kinase levels, was from 1.1 - 1.7% with telbivudine.[18] Creatine kinase levels were not part of the routine assessment in CHB management in normal daily practice; therefore, assessment of this particular side effect was not done in our study population.

Regarding its efficacy, our study showed similar benefit with previous studies (Globe and 2303 study). At week-52, HBeAg loss was found in 23.23% of the patient population while seroconversion was found in 14.14% of the patient population. This result is similar to what was shown in the 52 week Globe trial results (25.7% HBeAg loss and 22.5% seroconversion), respectively.[15] From these results, it can be concluded that telbivudine therapy is efficacious for CHB treatment in the Indonesian population.[19]

Undetectable serum HBV DNA levels by PCR at week-24 were similar with the results from the GLOBE trial, i.e. 45% in HBeAg-positive and 80% in HBeAg-negative patients. However, at week-52, our results were lower than the GLOBE trial which had PCR negativity of 60% in HBeAg-positive and 88.3% in HBeAg-negative patients.[15]

Early HBV DNA suppression during CHB treatment is important to predict long-term outcomes. A recent study of telbivudine in 117 treatment-naïve CHB patients (61.5% HBeAg-positive) showed that serum HBV DNA <200 IU/ mL at week 12 was predictive of favorable long-term outcomes, increase cumulative rates of HBeAg seroconversion, ALT normalization, and HBV DNA undetectability.[18]

In our study, 73.28% of patients who came for the last follow-up visit at week-52 showed normalization of serum ALT levels. In GLOBE trial, the rates of normalization of serum ALT at week-52 were reported more than 70% in patients treated with telbivudine.[15] After two-years, ALT normalization occurred in more than 80% of patients.[19]

Higher serum ALT levels at baseline could predict a higher rate of HBeAg seroconversion with long-term telbivudine therapy. HBeAg seroconversion was reported as high as 17.8% in patients with serum ALT <2x ULN, 32.3% in

patients with serum ALT 2-5x ULN, and 46.3% in patients with serum >5x ULN respectively.[20]

CONCLUSION

Telbivudine therapy is generally safe and well tolerated among adult Indonesian patients with chronic hepatitis B. Telbivudine is effective to produce HBeAg loss, seroconversion, suppress HBV DNA and normalization of serum ALT levels. In terms of efficacy measures, results from this study are comparable with results from the GLOBE trial.

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