Evaluation of One-Year Lamivudine and Telbivudine Therapy on Chronic Hepatitis B Patients: Based on Biochemical, Virological and Fibrosis Status in Dr. Soetomo General Hospital

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EVALUATION OF ONE-YEAR LAMIVUDINE AND TELBIVUDINE THERAPY ON CHRONIC HEPATITIS B PATIENTS: BASED ON BIOCHEMICAL, VIROLOGICAL AND FIBROSIS STATUS IN DR. SOETOMO GENERAL HOSPITAL

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Abstract

Background: *Lamivudine and telbivudine are still the recommended treatment for hepatitis B, especially in Indonesia. However, no conclusive results on evaluation of the lamivudine and telbivudine therapy in Dr. Soetomo hospital in one-year therapy.*

Objective: *To evaluate one-year Lamivudine and Telbivudine based on Hepatitis B Virus DNA, alanine aminotransferase, aspartat aminotransferase to platelet ratio index score, fibrosis-4, raid plasma reagin, platelet to lymphocite ratio score, transient elastography and liver biopsy.*

Methods: *This is analytic observational study and carried out by evaluating secondary data from medical record in Dr. Soetomo hospital.*

Results: *Significant decreased of Hepatitis B Virus DNA, normalization of alanine aminotransferase, improvement of aspartat aminotransferase to platelet ratio index, PLR and Transient elastography in one year each of lamivudine (p = 0.00; p=0.00; p = 0.00; p = 0.00; p = 0.00) and telbivudine group (p = 0.00; p=0.00; p = 0.00; p = 0.00; p =0.00). In HbeAg negative and positive patients, there were no significant different between lamivudine and telbivudine based on Hepatitis B Virus DNA reduction, normalization of alanine aminotransferase, improvement of aspartat aminotransferase to platelet ratio index score, fibrosis-4, platelet ratio index, transient elastography and liver biopsy. However, there was significant difference between lamivudine and telbivudine based on raid plasma reagin score in HBeAg positive patient (p = 0.013).*

Conclusion: *There were no significant difference between lamivudine and telbivudine one-year therapy based on biochemical, virological, and fibrosis status in Dr. Soetomo hospital.*

Keywords: *Chronic hepatitis B, Lamivudine, Telbivudine*

Introduction

Hepatitis B Virus (HBV) is a major public health problem. WHO estimates that in 2015, an estimated 257 million people, or 3.5% of the population were living with chronic HBV infection in the world, with higher prevalence found in developing countries including Indonesia. Left untreated, HBV infection can lead to cirrhosis (720000 deaths) and hepatocellular carcinoma (470000 deaths). These long-term complications are life-threatening and accounted for 96% of the deaths due to viral hepatitis [*WHO, 2017*]. In Indonesia, the number of people with hepatitis B infection is estimated to be 4.0-20.3% with the proportion of people outside Java island higher than the island of Java.

A nationwide study in 2013 revealed hepatitis B surface antigen (HBsAg) prevalence of 7.1%, which indicates that Indonesia has moved from high to moderate endemicity of hepatitis B [*Muljono D, 2017*]. In chronic hepatitis B infection, the

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main aim of the anti-viral therapy are to decrease morbidity and mortality by suppressing HBV replication and hepatic inflammation and preventing progression to cirrhosis and hepatocellular carcinoma. Anti-viral treatment results in normalization of alanine aminotransterase (ALT), suppression of HBV DNA, possible loss of HBsAg and seroconversion to anti-HBS, and also histological improvements with decreased inflammation and fibrosis. The Food and Drug Administration has approved seven anti-viral drugs for the treatment of chronic HBV: interferon a2b, pegylated interferon (PEG-IFN) alfa 2a, lamivudine (LAM), adefovir, entecavir (ETV), telbivudine (TDA), and tenofovir (*Syn*.tenofovir disoproxil fumarate - TDF). Of these, the most commonly used first-line agents are peg-IFN, TDF, and ETV [*Rajbhandari R, Chung RT, 2016*]. However, in developing country like Indonesia, Lamivudine and telbivudine still have widely used because they are low cost and had covered by government health insurance.

Lamivudine, a cytosine analogue, is the first nucleoside analog to be approved for the treatment of chronic hepatitis B. Lamivudine is effective in promoting HBeAg seroconversion, HBV DNA suppression, normalization of ALT and in decreasing the progression of liver fibrosis. However, treatment with lamivudine is limited by the development of viral resistance, with up to 68% of patients developing resistance after 4 years of treatment. Telbivudine is an L-nucleoside that is structurally related to lamivudine and highly selective for hepatitis B virus DNA and inhibits viral DNA synthesis [*Zhao S et al., 2010*].

Many studies compared the effectiveness one-year treatment of lamivudine and telbivudine in different community contexts. Systematic review by Zhao *et al* showed that telbivudine was better than lamivudine at the biochemical response, virological response, HbeAg loss, therapeutic response, while less than at the viral breakthrough and viral resistance, but no significant difference in the HbeAg seroconversion and HBsAg response [*Zhao S et al., 2010*]. The research conducted by [*Lai CL et al., 2007*] in adult, male and female patients, ages 16-70 years, in 2003-2004, with the administration of 600 mg telbivudine showed a higher decrease in HBV DNA compared to lamivudine, which was equal to -6.45% and –5.23% in patients with HBeAg positive and HBeAg negative [*Lai CL et al., 2007*].

In the present study, we investigated the effect of one-year lamivudine and telbivudine therapy in chronic hepatitis B who attended a hepatitis clinic in dr. Soetomo General Hospital Surabaya.

MATERIAL AND METHODS

This observational analytic study included ninety-three medical records of hepatitis B chronic adult patients who were registered in hepatitis clinic in Dr. Soetomo general hospital Surabaya during January 2011- December 2018. The diagnosis of hepatitis chronic was based on persistent HbsAg minimum for 6 months. These patients had negative or positive HBeAg and had received telbivudine 600 mg/day or lamivudine 100 mg/day continuously for one-year. These patient had complete data demographic (sex, age), laboratory (complete blood count (CBC) ALT, Bilirubin, Albumin), liver biopsy, and transient elastography before and after one-year therapy of lamivudine or telbivudine in medical record. We excluded patient who didn't have complete data in medical records. Virological status was determined by HBV DNA examination, the biochemical status seen with ALT and fibrosis status was measured by invasive (liver biopsy) and non-invasive methods with transient elastography.

AST to Platelet ratio index (APRI), Fibrosis-4 (FIB-4) Index, Platelet to lymphocyte ratio (PLR) and raid plasma reagin (RPR). HBV DNA loads were measured by quantitative real time PCR, and fibrosis score in liver biopsy were evaluated with METAVIR Scoring System. From these data, we also calculated noninvasive markers of liver fibrosis before and after one-year therapy, including APRI, FIB-4 index, PLR, RPR, based on the following formulas:

$$\text{APRI} = \text{AST x} \frac{\text{upper limit of normal AST}}{\text{platelets X 100}} \quad [6]$$

$$\text{FIB-4 index} = \frac{\text{age (years) x AST}}{\text{(platelets x ALT)}} \quad [7]$$

$$\text{PLR} = \frac{\text{Platelet}}{\text{lymphocyte count}} \quad [8]$$

$$RPR = \frac{RDW}{\text{platelet count}^{9}}$$

For statistical analysis this study used SPSS version 2.1 program. This study This study used unpaired T test to compare numeric data, which had normal distribution, and used Mann-Whitney test to compare numeric data, which had abnormal distribution.This study also used chi-square to compare nominal data. For pre and post evaluation, this study used paired T test analysis for numeric data, which had normal distribution, and used wilcoxon test for abnormal distribution.

RESULTS

Baseline Characteristic

Based on medical record data, it was found that total hepatitis B patients who met the inclusion criteria in 2011-2018 were 93 patients, the rest were excluded from the study due to incomplete data. Baseline characteristic patients are shown in table 1, it was found that the distribution of male diagnosed with hepatitis B was higher than that of female with a ratio of 1.7: 1. The mean age of patients diagnosed with hepatitis B was 49 ± 11 years old with a minimum age of 16 years old and a maximum of 79 years old.

The profile of analogue nucleoside therapy in hepatitis B patients was found to be more widely used by 70 patients (75.3%) while 23 (24.7%) patients used lamivudine. Based on total patients, 25 (26.9%) were diagnosed with Hepatic Cirrhosis and 38 (40.9%) patients were HBeAg positive.

Many hepatitis B patients treated in the Immune reactivation phase 54 (58.1%). Baseline data from biochemical markers were: Mean level of haemoglobin was 13.4 ± 2.0 *g/dL*, mean white blood cells count was (6.7 ± 2.4) x 10^9/*L*, mean platelet count was (6.7 ± 2.4) x 10^9/*L*, mean level of albumin was 4.1 ± 0.7 *g/dL*, mean level of ALT was 192.7 ± 194 *U/L* with highest value was 1129 *U/L* and lowest value was 13 *U/L*. Virologic data before treatment showed mean value of HBV DNA is 6.8 x 10^7 *IU/mL* with minimum value was 22 *IU/mL* and maximum value was 3.0 x 10^9 *IU/mL*. A biopsy was taken before and one-year after the treatment. The biopsy samples were reported based on METAVIR Score. Based on METAVIR score before the treatment, 48.4% (45) sample had F4 METAVIR score. Mean value of transient elastography was 17.1 ± 12.6 *kPa*, and mean value of APRI score was 2.0 ± 3.0.

In baseline characteristic based on HBeAg pos-

TABLE 1.

Baseline Characteristic Patients

	Frequency N= 93	Percentage (%)
Age (years old)	49 ± 11	
Sex:		
Male	40	42%
Female	53	53%
Nucleoside Analog Profile:		
Lamivudine	23	24.7%
Telbivudine	70	75.3%
Hepatic Cirrhosis:		
Yes	25	26.9%
No	68	73.1%
HBeAg Status:		
HBeAg positive	38	40.9%
HBeAg negative	55	59.1%
Phase:		
Immunetolerant	4	4.3%
Immune Active HBeAg+	32	34.4%
Inactive	3	3.2%
Immune Reactivation	54	58.1%
Virologic Marker:	Median (Min-Max)	
HBV DNA (*IU/mL*)	$3.5x10^6$ ($2.2x10^1$-$3.02x10^9$)	
Biochemical Marker:	Mean ± SD	
Hemoglobin (*g/dL*)	13.4 ± 2.0	
White Blood Cell (10^9/*L*)	6.7 ± 2.4	
Platelet (*x* 10^9/L)	192.7 ±194	
Albumin (*g/dL*)	4.1 ± 0.7	
ALT (*U/L*)	192.7 ±194	
Fibrosis status :		
Transient Elastography (*kPa*)	17.1 ± 12.6	
APRI Score	2.0 ± 3.0	
FIB-4 Index	2.7 ± 2.6	
PLR	0.02 ± 0.01	
RPR	0.10 ± 0.09	
Biopsy (METAVIR Score)		
F1	11	11.8%
F2	22	23.7%
F3	15	16.1%
F4	45	48.4%

NOTE: ALT - alanine aminotransterase, HBV - Hepatitis B Virus, HBsAg - hepatitis B surface antigen, PEG INF -pegylated interferon-a2alfa, APRI - AST to Platelet ratio index, FIB-4 - Fibrosis-4, PLR - Platelet to lymphocite ratio, RPR - raid plasma reagin.

TABLE 2.

Baseline Characteristic
Based on HBeAg Positive Patients

HbeAg Positive	LAMIVUDINE (n = 10)	TELBIVUDINE (n = 28)
Age:	52.6 ± 12.6	40.5 ± 10.4
	Frequency	
Sex :		
Male	7	20
Female	3	8
Hepatic Cirrhosis	5	22
HCC	0	0
Hepatitis C	0	0
HIV	0	0
Phase:		
Immunotolerant	2	2
Immuneactive	8	26
HbEAg +		
Liver Biopsy (METAVIR):	0	5
F1	2	5
F2	1	8
F3	7	10
F4		
	Median (min-max)	
HBVDNA (*IU/mL*)	1.1 x 10^8 (3.8x10^4 - 1.7x10^8)	1.03 x 10^8 (4.7x10^4-3.0x10^9)
APRI Score	1.09 (0.4-6.3)	1.39 (0.00-15.09)
FIB 4	2.84 (1.34-6.85)	1.51 (0.00-10.53)
RPR	0.1 (0.05-0.27)	0.06 (0.01-0.10)
PLR	0.01 (0.01-0.03)	0.01 (0.01-0.10)
Transient Elastography	23.3 (7.4-61.5)	11.5 (4.2-47.2)
Platelet (*x 10^9/L*)	178000 (73.700-291.000)	215500 (57200-510000)
Direct Bilirubin (*mg/dL*)	0.48 (0.11-4.74)	0.19 (0.08-6.14)
Total Bilirubin (*mg/dL*)	1.46 (0.11-4.74)	0.82 (0.28-7.19)
Albumin (*g/dL*)	4.03 (2.7-4.7)	4.15 (3.5-4.9)
ALP (*U/L*)	113.18 ± 116.72	104 (24-1062)
ALT (*U/L*)	127.54 ± 147.9	154 (28-1129)

NOTE: ALT - alanine aminotransterase, HBV - Hepatitis B Virus, HBsAg - hepatitis B surface antigen, PEG INF -pegylated interferon-a2alfa, APRI - AST to Platelet ratio index, FIB-4 - Fibrosis-4, PLR - Platelet to lymphocite ratio, RPR - raid plasma reagin, ALP - alkalin phoshate.

itive patient are shown in table 2, median value of HBV DNA in lamivudine group was 1.1 x 10^8 *IU/mL* with minimum value was 3.8x10^4 *IU/mL* and maximum value was 1.7 x 10^8 *IU/mL*. In telbivudine group, median value of HBV DNA was 1.03 x 10^8 *IU/mL* with minimum value was 4.7 x 10^4 *IU/mL* and maximum value was 3.0 x 10^9 *IU/mL*. Based on the METAVIR score, most of patients treated with lamivudine and telbivudine groups had F4 METAVIR score. FibroScan value in lamivudine group was 23.3 (7.4-61.5) *kPa* and telbivudine group was 11.5 (4.2-47.2) *kPa*. As for the APRI score, the lamivudine group obtained a median score of 1.09 (0.4-6.3) and in the telbivudine group the median score was 1.39 (0.00-15.09).

In baseline characteristic based HBeAg negative patients are shown in table 3, median value of HBV DNA in lamivudine group was 7.0 x 10^4 (4.2 x10^4 - 1.1 x 10^8) *IU/mL*, and in telbivudine group was 1.8 x 10^5 (2.9 x 10^4-1.1 x 10^8) *IU/mL*. Based on APRI score, in lamivudine group had median score was 0.8 with highest score was 5.63, and in telbivudine group median score was 0.6 with highest score was 14.12, transient elastography value in lamivudine group was 13.4 (2.00-42.30) *kPa* and telbivudine group was 14.05 (4.9-75) *kPa*. Liver biopsy showed 7 (53.8%) patients in lamivudine group had METAVIR score F4, and 10 (23.8%) patients in telbivudine group had METAVIR score F4.

One-Year Treatment Evaluation

Biochemical Status

According to ALT normalization, in total sample, there was significant different before and after one-year lamivudine therapy (p=0.00) and one-year telbivudine therapy (p=0.00). In the group that received lamivudine therapy with HBeAg positive, 100% (10) patients showed normalization of ALT, whereas in the group receiving telbivudine, 89.3% (25) patients showed normalization of ALT. However, in HBeAg positive patients, between lamivudine and telbivudine there was no significant different in normalization of ALT serum (p= 0.96). In HBeAg negative patients, who received lamivudine therapy, 13 (100%) patients showed ALT normalization, whereas in the group receiving telbivudine therapy, 92.9% (39) patients showed ALT normalization. However, there was no significant different in normalization of ALT between lamivudine and telbivudine after one-year therapy (p=0.14).

Virological Status

According to HBV DNA reduction, in total

TABLE 3.

Baseline Characteristic Based on HBeAg Negative Patients

HBeAg Negative	LAMIVUDINE (n = 13)	TELBIVUDINE (n = 42)
Age(year):	52.6 ± 12.6	53.12 ± 9.52
Sex :		
- Male	5	20
- Female	8	8
Hepatic Cirrhosis	5	22
HCC	0	0
Hepatitis C	0	0
HIV	0	0
Phase:		
- Inactive	1	2
- Immune Reactivation	12	26
Liver Biopsy (METAVIR Score):		
F1	2	5
F2	3	5
F3	1	8
F4	7	10
	Median (min - max)	
HBVDNA (*IU/mL*)	7.0 x 10^4 (4.2 x10^4 - 1.1 x 10^8)	1.8 x 10^5 (2.9 x 10^4-1.1 x 10^8)
APRI Score	0.8 (0.12-5.63)	0.6 (0.00-14.12)
FIB 4	2.11 (0.00-9.36)	1.71 (0.00-11.96)
RPR	0.08 (0.04-0.29)	0.07 (0.00-0.50)
PLR	0.01 (0.01-0.02)	0.01 (0.01-0.10)
Transient elastography	13.4 (2.00-42.30)	14.05 (4.9-75)
Platelet (*x 10^9/L*)	178000 (73.700-291.000)	203500 (74000-1230000)
Direct Bilirubin (*mg/dL*)	0.39 (0.09-8.95)	0.44 (0.03-4.60)
Total Bilirubin (*mg/dL*)	1.02 (0.3413.91)	0.81 (0.23-5.8)
Albumin (*g/dL*)	3.90 (2.80-10.00)	4.00 (3.60-4.70)
ALP (*U/L*)	57 (15-277)	67 (22-1062)
ALT (*U/L*)	79 (18-668)	86 (26-1022)

NOTE: ALT - alanine aminotransferase, HBV - Hepatitis B Virus, HBsAg - hepatitis B surface antigen, PEG INF -pegylated interferon-a2alfa, APRI - AST to Platelet ratio index, FIB-4 - Fibrosis-4, PLR - Pla-telet to lymphocite ratio, RPR - raid plasma reagin, ALP - alkalin phoshate.

sample, there was significant different before and after one-year lamivudine therapy (p=0.00) and one-year telbivudine therapy (p=0.00). In the group that received lamivudine therapy, the mean HBV DNA reduction was 6.1 x 10^7 *IU/mL*, with median reduction was 1.1 x 10^6 *IU/mL*. Meanwhile, in the group that received telbivudine therapy, the mean reduction in HBV DNA was 7.5 x 107 *IU/mL*, with a median 3.7 x 106 *IU/mL*. In HBeAg positive patients who recieved telbivudine therapy, showed 100% (28) patients had HBV DNA reduction. These result also seen in grup that recieved lamivudine therapy, that 100% (10) patients showed HBV DNA reduction. However In HBeAg postive and negative patients, after one-year therapy, there was no significant different in HBV DNA reduction between lamivudine and telbivudine therapy (in HBeAg positive patient: p=0.96, and in HBeAg negative patient: p=0.33).

Improvement of Fibrosis Status

According to improvement of fibrosis status, based on transient elastography, in total sample, there was significant different before and after one-year lamivudine therapy (p=0.00) and one-year telbivudine therapy (p=0.00). Based on APRI score, there was significant different before and after one-year lamivudine therapy (p=0.00) and one-year telbivudine therapy (p=0.00). These result also seen based on FIB4 index, there was significant different before and after one-year lamivudine therapy (p=0.03), but not in one-year telbivudine therapy, there was no significant different (p=0.08). Based on PLR, there was no significant different before and after one-year lamivudine

TABLE 4.

Comparison of One-Year Therapy with Lamivudine and Telbivudine after its treatnents

	HBeAg Positive			HBeAg Negative		
	Lam 100 *mg/day* N= 10	TDA 600 *mg/day* N=28	p Value	Lam 100 *mg/d day* N= 13	TDA 600 *mg/d day* N=42	p Value
Biochemical Status:						
Normalization ALT	100%	89.3%	=0.96	100%	92.9%	=0.14
Virological Status:						
HBV DNA Reduction	100%	100%	96%	92.3%	95.2%	=0.33
Improvement Fibrosis Status:						
Biopsy METAVIR Score	60%	78.6%	0.07	38.5%	66.7%	=1.00
Transient Elastography	100%	96.4%	0.10	92.3%	90.5%	=0.48
APRI	90%	85.7%	0.40	76.9%	59.5%	=0.32
FIB-4 Index	80%	82.1%	0.34	46.2%	54.8%	=0.57
PLR	40%	17.9%	0.71	7.7%	38.1%	=0.35
RPR	60%	71.4%	=0.04	69.2%	59.5%	=0.18

NOTE: ALT - alanine aminotransterase, Lam - lamivudine, TDA - telbivudine, HBV - Hepatitis B Virus, HBsAg - hepatitis B surface antigen, PEG INF -pegylated interferon-a2alfa, APRI - AST to Platelet ratio index, FIB-4 - Fibrosis-4, PLR - Pla-telet to lymphocite ratio, RPR - raid plasma reagin, ALP - alkalin phoshate.

therapy (p=0.37), but in telbivudine, there was significant different before and after therapy (p=0.02). Based on RPR, both lamivudine and telbivudine after one-year therapy, there was significant different (lamivudine: p= 0.02, telbivudine: p= 0.00).

In HBeAg positive patients, there was no significant different between lamivudine and telbivudine one-year therapy based on transient elastography (p=0.10), liver biopsy (p=0.07), APRI Score (p=0.40), PLR (p=0.71), and FIB4 index (p=0.34) as shown in table 4. However, there was significant different based on RPR (p=0.04). In HBeAg negative patients, there was no significant different between lamivudine and telbivudine therapy based on transient elastography (p=0.48), liver biopsy (p=1.00), APRI score (p=0.32), PLR (p=0.35), RPR (p=0.18), and FIB4 index (p=0.57).

DISCUSSSION

Based on the results of this study, it was found that the distribution of male diagnosed with hepatitis B was higher than female with a ratio of 1.7: 1 with an average age of 49 ± 11 years old. The results of this study were similar with a study conducted at RSUP Dr. Sardjito in Yogyakarta in 2017 10th erapeutic results and the effect of compliance against the results of therapy in patients with hepatitis B in the General Hospital Center (Dr, which shows hepatitis B infection is greater in male than female with ratio 1.8: 1 and the most patients infected with hepatitis B was 46-55 years old. HBV infection being higher in male and adult patient may be due to their greater exposures and interaction in society as compared to aged persons [*Khan et al., 2011*]. The profile of analog nucleoside therapy in hepatitis B patients was found that telbivudine was more widely used by 70 patients (75.3%) while 23 (24.7%) patients used lamivudin. When compared to effectiveness, telbivudine has better effectiveness than lamivudine. A 2005 study by Lai comparing the responses of one-year therapy to lamivudine and telbivudine, telbivudine exhibited significantly greater virology and biochemical responses compared with lamivudine ($p<0.05$) [*Lai C et al., 2005*].

Mean level of ALT before therapy was 192.7 ± 194 *U/L*, Virology data before treatment showed mean value of HBV DNA was $6.8 \times 10^7 \pm 3.1 \times 10^8$ *IU/mL*. This result is in accordance with the recommendations of the Indonesian Liver Research Association (PPHI) which recommends giving antiviral to patients with ALT levels more than 2 times upper normal limit and or HBV DNA $\geq 2 \times 10^4$ *IU/mL* in HBeAg positive patient and HBV DNA $\geq 2 \times 10^3$ *IU/mL* in HBeAg negative patients[13]. A biopsy was taken before and one-year after the treatment. The biopsy samples were reported based on METAVIR Score. Based on METAVIR score before the treatment, 48.4% (45) sample had F4 METAVIR score. Mean value of Transient elastography was 17.1 ± 12.6 *kPa*,

and mean value of APRI score was 2.0 ± 3.0. This result also in accordance with the recommendation by PPHI which recommended the provision of antiviral therapy for patients with significant fibrosis in liver biopsy characterized by METAVIR score F2 or liver stiffness calculated by transient elastography ≥ 8 *kPa* or APRI ≥ 1.5 [*PPHI, 2017*].

Some theories prove that telbivudine has greater efficacy compared to lamivudine. The molecular mechanism underlying the antiviral potency of telbivudine have not been fully elucidated; however, they may be associated with its observed preferential inhibition of second-strand HBV DNA synthesis or intracellular processes associated with its phosphorylation or interaction with the HBV polymerase [*Lai CL et al., 2005*]. But these results were different in this present study. After one-year treatment, based on biochemical, virology and fibrosis status measured by liver biopsy, transient elastography, APRI, PLR and FIb-4 score the present study showed that there was no significant different in both lamivudine and telbivudine groups seen in HBeAg positive and HBeAg negative patients. But based on RPR, there was significant different between lamivudine and telbivudine groups. These results were different with previously study conducted by [*Lai CL et al., 2005*] that showed Telbivudine had greater antiviral efficacy than did lamivudine in HBeAg positive and negative patients after one-year therapy [*Lai CL et al., 2007*]. Previous metaanalysis study also showed that at the end of one-year treatment, telbivudine was better than lamivudine at the biochemical response, virological response, HBeAg loss and theurapetic response[4]. The results of this present study were different probably due to the difference in the number of samples studied.

However, when analyzed by each group, both lamivudin and telbivudin showed significant differences before and after therapy. In patients with positive and negative HBeAg, there were significant differences before and after one-year therapy with lamivudin based on normalization of ALT, HBV DNA reduction, and fibrosis status assessed by transient elastography, APRI, FIB-4 Index, and RPR. This result similar to pevious study conducted by [*Fung SK et al., 2004]*, showed that in HBeAg negatif patients, lamivudine had high initial response rate with 88% and 92% achieving undetectable HBV DNA by PCR and hybrid capture assay at month 12 [*Fung S et al., 2004*]. This present study showed, in HBeAg negative patients 84.6% had undetectable HBV DNA at month 12. There were also significant differences before and after one-year therapy with telbivudine based on normalization of ALT, HBV DNA reduction, and fibrosis status assessed by transient elastography, APRI, PLR, and RPR. This study similar to previous study that showed at one-year treatment, significant reduction in HBV DNA in telbivudine therapy in HBeAg positive and HBeAg negative was observed [*Jones R, Nelson M, 2006*]. This result may be due to due to low HBV DNA levels pretreatment where the effectiveness of lamivudine and telbivudine are best obtained at HBV DNA levels < 2 x 10^8 *IU/ml* and ALT >2x upper normal limit before therapy.

The limitation of this study lies in the recording of medical records that is not filled in completely, so the researcher is forced to exclude a number of incomplete data. Filling out patient resumes and completing a good medical record will help further research, so that the results of research can be more representative in the population.

CONCLUSION

There were no significant difference between lamivudine and telbivudine one-year therapy based on biochemical, virological, and fibrosis status in Dr. Soetomo General Hospital. However, in each grup either lamivudine or telbivudine, there were significant different based on biochemical, virological, and fibrosis status before and after one-year therapy. So telbivudine and lamivudine are still effective as hepatitis B treatment in developing country like Indonesia. There were no significant difference between Lamivudine and telbivudine one-year therapy based on biochemical, virological, and fibrosis status in Dr. Soetomo General Hospital. However, in each grup either lamivudine or telbivudine, there were significant different based on biochemical, virological, and fibrosis status before and after one-year therapy. Therefor, telbivudine and lamivudine are still effective as hepatitis B treatment in developing country like Indonesia.

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