Antiviral Treatment and One-year Follow-up of Chronic Hepatitis B Patients in Bandung: An Observational Study

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ABSTRACT

Background: *Hepatitis B virus (HBV) is a health problem that has chronically infected 257 million globally. Appropriate therapy is immensely needed to prevent disease progression to cirrhosis and hepatocellular carcinoma (HCC). Moreover, routine monitoring is required to assess the efficacy of the given treatment. This study aims to describe the treatment and its follow-up outcomes among chronic HBV patients after one year of therapy in Bandung.*

Method: *This was a cross-sectional descriptive study with a data sampling method obtained from assessing the medical records of treated chronic HBV outpatients at the Gastrohepatoenterology Clinic of Hasan Sadikin Hospital Bandung from 2018 to 2020. Laboratory findings before and after one year of therapy were further assessed.*

Results: *Out of 107 patients treated, the proportion of tenofovir was 72.90%, telbivudine 16.80%, lamivudine 8.40%, and interferon group 1.90%. There were 52.30% of patients who did follow-up visits after one year of therapy. The therapeutic outcome rate was evaluated among total patients with the criteria of decreasing aspartate aminotransferase (AST) (91.18%) and alanine aminotransferase (ALT) levels (93.10%) levels, reduction of hepatitis B virus deoxyribonucleic acid (HBV-DNA) values (100%), and hepatitis B e antigen (HBeAg) seroconversion (14.29%).*

Conclusion: *The most given therapy among chronic HBV outpatients was tenofovir. The follow-up rate of patients after one year of treatment was 52.30%. Overall, antiviral therapies produced decreases in liver laboratory parameters, HBV-DNA, and HBeAg.*

Keywords: *Antiviral therapy, hepatitis B e antigen (HBeAg), hepatitis B virus deoxyribonucleic acid (HBV-DNA), hepatitis B virus*

ABSTRAK

Latar belakang: *Hepatitis B merupakan masalah kesehatan yang serius di mana sekitar 257 juta penduduk dunia terinfeksi virus ini secara kronis. Terapi yang tepat sangat diperlukan untuk mencegah perkembangan penyakit menjadi sirosis dan hepatocellular carcinoma (HCC). Selain itu, terapi harus dipantau untuk menilai*

efektivitas pengobatan. Penelitian ini bertujuan untuk mengetahui jenis terapi dan hasil follow-up pasien hepatitis B kronik pasca satu tahun terapi di Bandung.

Metode: *Penelitian deskriptif potong lintang dengan metode total sampling menggunakan kajian rekam medis pasien rawat jalan hepatitis B kronik yang diterapi di Poliklinik Gastrohepatoenterologi RS Hasan Sadikin Bandung pada periode 2018-2020. Hasil laboratorium sebelum dan setelah satu tahun terapi kemudian dinilai lebih lanjut.*

Hasil: *Dari 107 pasien yang diterapi, proporsi tenofovir sebesar 72,90%, telbivudin 16,80%, lamivudin 8,40%, dan golongan interferon 1,90%. Terdapat 52,30% pasien yang melakukan follow-up setelah satu tahun terapi. Tingkat keberhasilan hasil terapi dievaluasi dari total sampel dengan kriteria penurunan kadar aspartate aminotransferase (AST) (91,18%) dan kadar alanine aminotransferase (ALT) (93,10%), penurunan nilai deoxyribonucleic acid virus hepatitis B (100%), serta serokonversi hepatitis B e antigen (HBeAg) (14,29%).*

Simpulan: *Terapi yang paling sering diberikan pada pasien rawat jalan hepatitis B kronik adalah tenofovir. Tingkat follow-up pasien setelah 1 tahun terapi sebesar 52,30%. Secara keseluruhan, terapi antivirus menghasilkan penurunan pada parameter laboratorium hati, HBV DNA, dan HBeAg.*

Kata kunci: *hepatitis B e antigen (HBeAg), hepatitis B virus deoxyribonucleic acid (HBV DNA), hepatitis B virus, terapi antivirus*

INTRODUCTION

Hepatitis is an inflammatory liver disease generally caused by viral infection.[1,2] It is still one of the leading health problems in the world, including in Indonesia.[3] According to World Health Organization (WHO) data collection in 2015, around 257 million people, or 3.5% of the world's population, were chronically infected with hepatitis B virus (HBV). Chronic HBV is defined as the occurrence of hepatitis B surface antigen (HBsAg) for six months or more. It causes the most prevalent mortalities compared to other types of hepatitis viruses.[4,5]

Indonesia is classified as a high chronic HBV infection rate category.[6] HBV patients in healthy Indonesian populations are estimated to be 4.0-20.3%.[7–9] Chronic HBV therapy is given based on indications of serum hepatitis B virus – deoxyribonucleic acid (HBV-DNA) values, Hepatitis B e Antigen (HBeAg) status, alanine aminotransferase (ALT) level, and liver histology. Currently, two drugs can be given as a preferred medication for HBV cases, the interferon group (pegylated interferon α-2a 90-180 µg once a week or pegylated interferon α-2b 1-1,5 µg weekly) and nucleos(t)ide analogs (lamivudine 100 mg, adefovir 10 mg, entecavir 0.5 mg or 1 mg, telbivudine 600 mg, and tenofovir 300 mg).[8]

The accuracy and suitability of hepatitis treatment will improve patients' prognosis and quality of life.[10] Chronic HBV can develop into advanced liver diseases such as cirrhosis or hepatocellular carcinoma (HCC), a leading cause of death in HBV patients if not given the proper treatment.[4] However, recent studies on chronic HBV therapy and its follow-up are still limited. This study aims to describe the type of therapy and its follow-up outcomes in chronic HBV patients.

METHOD

This was a cross-sectional descriptive study conducted between October and November 2021. Data in our study were collected from medical records of treated chronic HBV outpatients at the Gastrohepatoenterology Clinic of Hasan Sadikin General Hospital, Bandung, from January 1, 2018, to December 31, 2020. The inclusion criteria were patients over 18 years old and positive HBsAg for at least six months. However, patients co-infected with human immunodeficiency virus (HIV) or chronic kidney disease (CKD) stage 3-5 comorbid were excluded from the study. The research was conducted after receiving permission from the Research Ethics Committee of the Universitas Padjadjaran and Dr. Hasan Sadikin General Hospital Bandung.

Data analysis was summarized using Microsoft® Excel 2016. The features of HBV patients such as gender distribution, duration of diagnosis, age, platelets level, hemoglobin level, hematocrit level, and leukocytes level were recorded. The patient's age was calculated from birth to once the patient was diagnosed with HBV. The duration of diagnosis was the time measured from the patient's first initial diagnosis of HBV until the therapy was given, which was grouped into two categories, namely less than one year (< 1 year) and more than one year (≥ 1 year). The type of therapy was divided into categories of interferon and four subcategories

of the nucleos(t)ide analogs (lamivudine, tenofovir, entecavir, and telbivudine).[8] We assessed the follow-up rates after one year of therapy through the patients' medical records and summarized the successful outcome rates from aspartate aminotransferase (AST), alanine aminotransferase (ALT), HBV-DNA, and HBeAg seroconversion measurements. The results were further presented in tables to outline the baseline characteristics, type of therapy, one-year follow-up rates, and therapeutic outcome rates after one year of treatment.

RESULTS

A total of 111 patients with HBV were given therapy from January 1, 2018, to December 31, 2020. One patient had coinfection with HIV, and three patients who had CKD grades 3-5, were excluded from the study. Subsequently, 107 subjects were included in this study.

Table 1 summarizes our study's baseline characteristics of chronic HBV patients (n = 107). Most patients were males (66.3%), while 33.7% were females. Most of the patients were treated during their first HBV diagnosis (n = 89). All laboratory parameters of thrombocyte, hemoglobin, hematocrit, and leukocyte levels were normal.

Table 2 depicts the types of antiviral therapy consumed by chronic HBV patients at the Gastrohepatoenterology Clinic of Hasan Sadikin General Hospital Bandung from 2018 to 2020. All patients were treated based on the indication stated by the Indonesian Association for the Study of the Liver (Perhimpunan Peneliti Hati Indonesia, PPHI). Nucleos(t)ide analogs were more frequently used therapy compared to interferon, with tenofovir being the most preferred one (72.9%), followed by telbivudine (16.8%) and lamivudine (8.4%). Our study showed no use of entecavir as an antiviral therapy because most patients took Indonesia health insurance (BPJS) that did not cover entecavir. On the other hand, only two patients received interferon therapy, and both were in 2018. After a year, one of them was converted to tenofovir therapy because the HBV DNA target was not achieved. During treatment, two patients who initially received telbivudine had a tenofovir replacement on the seventh and 12th months after initial therapy because of telbivudine discontinuation from the principal. Most telbivudine therapy patients were in 2018 until the middle year of 2020. In the past few years, most patients were treated with tenofovir.

Table 1. Characteristics of chronic hepatitis B virus (HBV) patients

Variable	Chronic HBV patients (n = 107)	
	n	%
Gender		
Male	71	66.3
Female	36	33.7
Duration of diagnosis		
< 1 year	89	83.2
≥ 1 year	18	16.8
	Average (x)	**Standard deviation (s)**
Age (years)	43.9	12.27
Thrombocyte (10^3/uL)	199.75	126.62
Hemoglobin (g/dL)	13.5	2.12
Hematocrit (%)	41	11.31
Leukocyte (10^3/uL)	6.23	2.02

Table 2. Types of antiviral therapy for chronic hepatitis B virus (HBV) patients

Antiviral therapy	Chronic HBV (n = 107)
	n (%)
Nucleos(t)ide Analogues	
Lamivudine	9 (8.4)
Tenofovir	78 (72.9)
Entecavir	0 (0.0)
Telbivudine	18 (16.8)
Interferon	2 (1.9)

Table 3. One-year follow-up rates among treated chronic hepatitis B virus (HBV) patients

Variables	Chronic HBV patients (n = 107) n (%)
Patients who lost to follow-up after 1-year therapy	51 (47.7)
Patients who did follow-up after 1-year therapy	56 (52.3)

Table 3 shows one-year follow-up rates among treated chronic HBV patients. Only more than half of the patients (52.3%) went back to the outpatient clinic after one year of therapy, while the rest, 47.7%, were lost to follow-up. Of the 56 patients who did follow-up visits, 98.2% had AST and ALT measurement, 50% underwent HBeAg check-ups. While HBV DNA and HBsAg were less frequently checked (33.9% and 26.7%, respectively).

Overall, antiviral therapies produced remarkably decreases in liver laboratory parameters and HBV DNA (Table 4). There were 34 patients with abnormally high AST values from the initial treatment. After one year, 91.2% of those patients (n = 31) had a reduction in AST values, in which 20 patients had AST progressively declined to normal range. For the ALT examination, 27 out of 29 patients had a decreased level than their previously high values (20 patients reached the expected values). Other patients with normal initial ALT and AST levels were treated with liver fibrosis evidence.

Table 4. One-year follow-up rates among treated chronic hepatitis B virus (HBV) patients

Laboratory findings	Chronic HBV patients after 1 year of therapy (n = 56) n (%)
AST	55 (98.2)
ALT	55 (98.2)
HBV - DNA	19 (33.9)
HBeAg	28 (50.0)
HBsAg	15 (26.8)

AST: aspartate aminotransferase, ALT: alanine aminotransferase, HBV-DNA: Hepatitis B virus deoxyribonucleic acid, HBeAg: Hepatitis B e-antigen, HBsAg: Hepatitis B surface antigen

Table 5. Therapeutic outcomes rates of treated chronic HBV patients

Outcomes	n	a/b (%)
Decrease in AST	31	31/34 (91.2)
Decrease in ALT	27	27/29 (93.1)
Decrease in HBV DNA	19	19/19 (100)
HBeAg seroconversion to HBeAg (-)	2	2/14 (14.3)
HBeAg (+) to equivocal	3	3/14 (21.4)
HBsAg loss within one year	0	0/15 (0.0)

AST: aspartate aminotransferase, ALT: alanine aminotransferase, HBV-DNA: Hepatitis B virus deoxyribonucleic acid, HBeAg: Hepatitis B e-antigen, HBsAg: Hepatitis B surface antigen, a (numerator): number of patients with successful outcomes from a specific parameter, b (denumerator): number of patients checked for a specific parameter after a year of therapy with high initial results

Nineteen patients were detected HBV-DNA before a treatment based on the PCR results. All those patients showed a successfully decreased pattern after one year, of which 13 patients converted into non-reactive HBV-DNA. Additionally, 14.3% of patients with prior reactive HBeAg had fully seroconverted after therapy (2 out of 14 patients), whereas nine patients were classified as reactive and three patients as equivocal.

Table 5 describes the response rates of each antiviral treatment based on laboratory parameters after one year of medication. Tenofovir and Telbivudine resulted in good outcomes among chronic HBV patients with positive HBeAg after one year of therapy. Tenofovir caused all 14 patients to have AST and ALT levels decreased, 5 out of 8 patients with undetected HBV-DNA, and 1 out of 12 with HBeAg seroconversion. Similarly, Telbivudine also produced a decline of AST and ALT in all four patients, 50% incidence of HBeAg seroconversion in 2 patients, but no improvement regarding HBV-DNA. In comparison, there were no follow-up visits of patients receiving lamivudine and interferon to support the data.

We found that Lamivudine and Interferon had good outcomes in patients with negative HBeAg. After one year, the only patient treated with lamivudine therapy progressed to have improvements in AST, ALT, and HBV-DNA status (100%). This finding was also found in a patient receiving interferon who had undetected HBV DNA. Tenofovir lowered AST levels in 8 out of 10 patients, and 5 out of 6 patients had lower ALT and undetected HBV-DNA. Whereas 80% of patients declined in AST, 50% had lower ALT, and 50% had undetected HBV-DNA in the group treated with Telbivudine.

DISCUSSION

The gender distribution among treated chronic HBV outpatients at the Gastrohepatoenterology Clinic of Hasan Sadikin Hospital Bandung from 2018 to 2020 was dominated by males (66.3%) compared to females (33.7%). A similar study conducted by Baig et al. found a gender difference in HBV infection counted as much as 79.5% in men and 20.5% in women (male to female ratio of 4:1). The reason behind this discrepancy was probably caused by the alcohol and cigarettes consumption rates, which are generally higher in males, and the effects of the estrogen hormone as a protection or defense mechanism of hepatocytes towards the progression of chronic liver disease in women.[11]

HBV is transmitted through exposure to infected blood or body fluids. Transmission can occur vertically from mother to child, which is the leading cause of HBV infections, or horizontally through blood transfusions, the use of unsterile needles, and sexual activity with an infected partner.[12–14]

Table 6. Response rates (%) after one-year antiviral therapy of chronic HBV patients based on antiviral drugs

Variables	Tenofovir	Telbivudine	Lamivudine	Interferon
Patients with hepatitis B e antigen (HBeAg) (+)				
Decrease in aspartate aminotransferase (AST)	100%	100%	-	-
Decrease in alanine aminotransferase (ALT)	100%	100%	-	-
Undetected HBV DNA	62.5%	0%	-	-
HBeAg (+) seroconversion to HBeAg (-)	8.3%*	50%	-	-
HBeAg (+) to equivocal	25%	50%	-	-
Patients with HBeAg (-)				
Decrease in AST	80%	80%	100%	-
Decrease in ALT	83.3%	50%	100%	-
Undetected HBV DNA	83.3%	50%	100%	100%

*The result came due to lack of documented HBeAg on medical records

Duarte-Rojo et al in 2010, concluded that tenofovir has a relatively good safety profile and remarkable antiviral properties. More patients were treated with nucleos(t)ide analogs than the interferon group with the highest percentage on tenofovir (72.9%).[15] Consistent with the previous study, tenofovir has an excellent resistance profile and is recommended for patients resistant to other therapies.[8,16,17] Therefore, based on clinical effectivity, tenofovir is preferred in patients with chronic HBV.

The hepatotoxicity effect of this antiviral therapy, especially tenofovir (the most given treatment), is not significant, with evidence of more than 90% of a year treated patients resulting in good outcomes in reducing the liver function parameter (ALT and AST). In convincing reports, a similar study reported little or no direct hepatotoxicity attributable to tenofovir with no clinical occurrence of acute liver injury.[18]

This study also reports that after one year of tenofovir therapy among chronic HBV patients with positive HBeAg, 100% had a decline in AST and ALT, 62.5% had undetected HBV DNA, and 8.3% had HBeAg seroconversion. Likewise, this one-year course of tenofovir therapy in chronic HBV patients with negative HBeAg showed that 80% of patients got a decrease in AST, and 83.3% got a reduction in ALT as well in HBV DNA. These findings are supported by a similar study by Scaglione et al., which showed that post 48-52 weeks of tenofovir therapy in chronic HBV patients with positive HBeAg yielded the normalization of the ALT (77%) and undetected HBV DNA (76%). While in the negative HBeAg group, 93% of patients were stated to have undetected HBV DNA.[19] Another study conducted by Fung et al noted that the rate of HBeAg seroconversion among chronic HBV treated with tenofovir after 48-weeks tenofovir therapy was 8%, similar to our result in this study.[20]

Our study showed that among the chronic HBV patients with positive HBeAg treated with telbivudine for a year, 100% had decreased in AST and ALT levels, 0% had undetected HBV DNA, and 50% had HBeAg seroconversion. Patients with negative HBeAg that were treated with telbivudine for a year showed a decrease in AST level (80%), a reduction in ALT level (50%), undetected HBV-DNA (50%). A similar study by Jules et al stated that telbivudine-used for chronic HBV patients with positive HBeAg got a 77% in ALT normalization frequencies at one-year therapy.[21] Another study conducted by Hou et al found that in patients with chronic HBV with positive HBeAg after 48 to 52 weeks of telbivudine therapy, 60% had HBV-DNA undetectable, and 22% had seroconversion of HBeAg. Whereas, in patients with negative HBeAg, 74% had normalization of ALT, and 88% had undetected HBV-DNA.[22] Interestingly, the result of our positive HBeAg receiving-telbivudine patients after one year of therapy did not follow the previous research. This happened because of the incompleteness of medical records and the small number of patients treated with telbivudine within measured years. Only one treated patient with telbivudine followed up HBV-DNA examination after one year of therapy, and the result was still reactive. Thus, making the percentage of undetected HBV-DNA among telbivudine-treated patients with positive HBeAg in this study was 0%.

This one-year course of lamivudine treatment in chronic HBV patients with negative HBeAg resulted in high AST, ALT, and HBV-DNA reduction (100%). A previous study by Scaglione et al also produced a similar result, where 60-73% of undetected HBV-DNA among chronic HBV patients with negative HBeAg after 48 to 52 weeks treated with lamivudine.[19] Study of biochemical endpoints at week 48 lamivudine-used conducted by Lai et al were showed that 71% of patients got ALT normalization.[23]

Reported on this study, the percentage of undetected HBV-DNA after a one-year course of interferon treatment was 100%. In contrast, research by Kwon et al found that only 25% of patients had a decrease in HBV-DNA after 48 to 52 weeks of therapy with interferon.[24] The different results between these two studies occur due to the lack of samples treated interferon and the low compliance of patients to follow-up with their physicians during treatment.

The limitations of our study were the study design from secondary data that resulted in no guarantee of complete data variables. Furthermore, a relatively high lost follow-up rate (47.7%) may be due to the unaffordable cost of HBV-DNA and HBeAg examination, that partially covered by the Indonesian health insurance or badan penyelenggara jaminan sosial (BPJS).

CONCLUSION

Tenofovir was the most given therapy among chronic HBV outpatients at the Gastrohepatoenterology Clinic of Hasan Sadikin Hospital, Bandung. The follow-up rate of patients after one year of treatment was 52.3%. Overall, most antiviral treatments decreased liver laboratory parameters, HBV-DNA, and seroconversion of HBeAg.

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