J Surg Med. 2022;6(3):246-249.
DOI: 10.28982/josam.1076437

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of chronic hepatitis B patients receiving lamivudine: Single center experience

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Ethics Committee Approval
Ethics committee approval of this study was obtained on 19.01.2022 with decision number 2022-3 from the Clinical Studies Ethics Committee of Medical Faculty at Hitit University. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2022 March 15

Abstract

Background/Aim: Lamivudine (LAM), which has been used for the treatment of Chronic Hepatitis (CHB) infection for many years, is now provided for short-time use to immunosuppressive patients due to resistance. We aimed to evaluate the current state and pandemic period routine follow-ups in patients who still used LAM today due to treatment or prophylaxis in terms of virologic or serologic treatment response.
Methods: In this retrospective cohort study, we included 33 patients who received LAM treatment or prophylaxis due to CHB. Evaluations included patients' serologic results for Hepatitis B, platelet counts, comprehensive metabolic panel, HBV DNA levels, ultrasonographic (USG) evaluation of the liver, and the number and duration of outpatient visits between 01.01.2020 and 31.12.2021.
Results: Of all the patients, 51.5% (n=17) were males, and the average age was 57.3 (12.3) years. The median LAM treatment duration was found 10 (2.58) years. The ratio of receiving LAM due to immunosuppressive therapy was 27.27% (n=9). Except for HBV DNA-negative patients or patients with no accessed results, the virologic response rate of patients was found 60.7% (n=20). Within the study period, while Anti-Hbe seroconversion was found 3.2% (n=1), Anti-Hbs seroconversion was found 6.5% (n=2). One patient whose virologic response was not obtained, received the treatment without any alterations in the regimens. While the number of outpatient follow-ups in the study period was found 1.94 (0.24) on average, the duration between follow-ups was found 13.82 (12.8) months.
Conclusion: It is pleasing to obtain virologic response and Anti-HBs, Anti-HBe seroconversion in patients with low resistance profile who receive the LAM treatment. While watchful waiting is recommended for patients receiving long-term LAM treatment, our retrospective analysis showed that planned outpatient follow-ups for every three months was done in longer intervals. The treatment is not altered in one patient whose virologic response was not obtained because of inadequate number of follow-ups within the study period. Since monitoring without having prolonged follow-up durations due to the pandemic is of importance in terms of preventing complications, we believe that there is a need for further studies on this issue.

Keywords: HBV DNA, Chronic hepatitis B, Lamivudine, Seroconversion, Seroclearance, Pandemic

How to cite: Yapar D, Akdoğan Ö. Evaluation of chronic hepatitis B patients receiving lamivudine: Single center experience. J Surg Med. 2022;6(3):246-249.

Introduction

The WHO reports that around 296 million people live with the chronic Hepatitis B (CHB) infection, with 1.5 million new cases added every year [1]. Although our country is known as medium-level endemic for the Hepatitis B (HBV) virus, one in every three adults is reported to have HBV exposure [2]. The main purpose of the CHB treatment is to suppress HBV DNA levels with undetectable levels, which aims to prevent complications such as cirrhosis and hepatocarcinoma (HCC) [3]. Nowadays, nucleos(t)ide analogs are used to suppress viral replication. These antivirals used in CHB treatment are generally well tolerated. It is unknown how long these treatments would be provided, because usually they can be used for a long time without severe side effects. Lamivudine (LAM), which has been used since 1998, is a nucleoside analog with moderate strength. After a five-year application, it could cause high levels of treatment failure with high resistance levels around 80% [4, 5]. While the world has been fighting the COVID-19 pandemic since December 2019, there have been disruptions particularly in the blood tests and treatment of patients with chronic diseases. In this regard, both COVID-19 and CHB management have been very much affected by these difficult processes in patients with CHB [6, 7]. In this study, we aimed to evaluate the number of outpatient visits currently and especially during pandemic, in patients receiving the LAM treatment for CHB.

Materials and methods

This retrospective cohort study included patients who were prescribed LAM due to CHB and visited the Infectious Diseases outpatient clinic between 01.01.2020 and 31.12.2021.

Patients who received other antiviral treatments for CHB or those below 18 were excluded. Patients' demographic data, additional diseases, HBsAg, HBeAg, Anti-HBs, Anti-HBe results, hemogram parameters, AST-ALT-bilirubin and alpha-fetoprotein (AFP) values, HBV DNA levels, USG images of the liver at the beginning of the treatment and in last follow-up were evaluated. While HBsAg/HBeAg loss was defined as seroclearance, the development of Anti-HBs/Anti-HBe was defined as seroconversion. Negative-HBV DNA for virologic response was defined as an HBV DNA level of below 50 IU/ml. Detection of granular appearance was defined as progression, if it was undetected in the first USG imaging**.** Patients' routine follow-up duration was accepted as three months. The duration between the number of patients' outpatient visits between 01.01.2020 and 31.12.2021 and the duration between these visits during the pandemic was evaluated as months. Nucleic acid isolation for HBV DNA was performed using the Magnesia16 (Anatolia Geneworks, Turkey) device. The quantitative HBV DNA tests were conducted using the Montania4896 (Anatolia Geneworks, Turkey) device using real-time polymerase chain reaction (RT-PCR) in accordance with the manufacturer's instructions.

Statistical analysis

Data were analyzed using IBM SPSS 23.0 (SPSS Inc., Chicago, IL, USA) licensed by Hitit University. Data of continuous variables were expressed as mean, standard deviation and data of categorical variables were expressed as percentages. In the analyzes comparing the two groups, Mann-Whitney U test was used for continuous variables, Chi-square test and Fisher exact test were used for categorical variables, and Spearman correlation test for correlations.

Ethics

Ethics committee approval of this study was obtained on 19.01.2022 with number 2022-3 from the Clinical Studies Ethics Committee of Medical Faculty at Hitit University. The study followed the ethical principles indicated in the Declaration of Helsinki at all stages.

Results

This study included 33 patients who received LAM treatment. Of all these patients, 51.5% (n=17) were males, and the average age was 57.3 (12.3) years (32-78 years). The patients' comorbid were analyzed, which included hypertension (HT) in 24.2% (n=8), diabetes mellitus (DM) in 9.1% (n=3), rheumatologic diseases in 15.2% (n=5), chronic kidney failure (CKF) in 9.1% (n=3), kidney transplantation in 6% (n=2), multiple myeloma (MM) in 3% (n=1), breast cancer in 3% (n=1), and coronary artery disease (CAD) in 3% (n=1). Of all the cases, 27.3% (n=9) were receiving immunosuppressive treatment for different reasons. The median duration of LAM treatment was 10 (2.58) years. Table 1 demonstrates patients' ALT, total protein, albumin, total bilirubin, platelet, AFP, HBV DNA levels, and serologic results. In the beginning of the treatment period, average HBV DNA viral load of 69.7% (n=23) of the patients was 79,9026 IU/ml (131-16,000,000 IU/ml). While 21.3% (n=7) of the patients had negative HBV DNA, the HBV DNA results of 9% of the patients could not be accessed. According to the last HBV DNA evaluated, they were negative in 84.8% (n=28). Virologic response could not be obtained in a patient with HBV DNA 578 IU/ml. USG imaging of this patient indicated no liver cirrhosis. Results of 12.1% (n=4) patients could not be accessed. In the beginning, except for HBV DNA negative patients or patients with no accessed results, the virologic response rate of patients was found 60.7% (n=20).

Table 1: Patients' demographic features and laboratory values

Variable	Value	
Age (mean (SD)) (year)	57.3 (12.3) (32-78)	
Sex (n; %)	Male (17; 51.5%)	
Treatment period (years)	10 (5-15)	
	Laboratory findings at the beginning of treatment	Laboratory findings at the last follow-up
ALT (IU/L)	25.46 (14.73)	20.7 (12.37)
T. protein (mg/dL)	7.52 (0.98)	7.12 (8.66)
Albumin (mg/dL)	4.46 (0.61)	4.07 (3.8)
T. bilirubin (g/L)	0.94 (1.27)	0.73 (0.31)
Platelet (mm^3/L)	229.3 (71.9)	216.55 (81.97)
AFP	2.34 (1.67)	2.42 (1.39)
HBV-DNA (IU/mL)	799,026 (31-16,000,000)	136 (16-578)
HBeAg loss or seroconversion (n,%)		1 /31 (%3.2)
HBsAg loss or seroconversion (n,%)		2/31 (%6.5)

SD: Standard deviation, AFP: Alpha fetoprotein ALT: Alanine aminotransferase

Before the treatment, HbeAg was positive in only one patient, whereas the results of two patients could not be accessed. All other patients were positive for Anti-Hbe, which confirms that HbeAg-positive patients under treatment developed Anti-HBe seroconversion. Anti-Hbs seroconversion was determined as 6.5% (n=2).

Table 2 demonstrates the analysis of the USG findings of the liver at the beginning and in last follow-up of the treatment. From four patients not having initial USG results, two

patients had normal USG imaging, whereas remaining two had granular appearance.

Table 2: Findings in the USG imaging of the liver

	USG findings at the beginning of treatment % (n=29)	USG findings at the last follow-up % (n=33)
Normal	41.4 (12)	30.3 (10)
Hepatosteatosis	27.6 (8)	18.2 (6)
Granular appearance	24.1 (7)	45.5 (15)
Hepatomegaly	6.9 (2)	6.1 (2)

USG: Ultrasonography

During the study period, the average number of follow-up visits was 1.94 (0.24) and the average duration between follow-ups was 13.81 (1.28) months. The ratio of the delays in the routine follow-ups was 100% within the last two years. The duration between the last follow-up visits before and during the pandemic was found to be 11 (0-30) months on average.

Discussion

Globally, LAM had been the only option for the treatment of CHB for a long time. With the launch of new treatments with high resistance barriers, LAM is mainly transformed into short-term use in patients receiving immunosuppressive treatment [8]. Until recently, the first treatment option for CHB patients was supposed to be LAM or telbivudine (LdT) if their HBV DNA level was $<10^7$ IU/mL, according to the Communique on Healthcare Practices (CHP) in Turkey. With the changes in the treatment options in guidelines, treatments in Turkey have also been updated. We, therefore, aimed to evaluate the current state of patients who still used LAM nowadays.

A study that monitored the long-term outcomes of the LAM treatment, reported patients' duration of LAM use median as 16.1 (3.2-19.5) years [9]. In our study, this duration was found 10 (2.58) years. Shorter duration of LAM might be because we have been performing the follow-up of patients with CHB in our department for approximately 15 years. Initial serum biochemical, platelet, and AFP values of our patients were within normal ranges, and the last evaluations were also found to be similar with the compared study.

When the patients' HBV DNA levels were analyzed, virologic response could not be obtained in one patient. This patient was found to have findings of cirrhosis in the liver biopsy that was done before the treatment. Severe results developed under long-term treatment with nucleoside analogues, especially, patients with negative HBeAg were found to have cirrhosis of the liver in the beginning [4]. This patient's HBV DNA level was negative under treatment, but it was still high in the last evaluation, which refers to the resistance developed against LAM. Unfortunately however, when the data belonging to this patient were analyzed, it was found that the patient had not been administered test or a more potent treatment yet, due to LAM resistance. Except for HBV DNA-negative patients or patients without accessed results, the virologic response rate of patients was found to be 60.7% (n=20), in the beginning. While a study that evaluated a five-year LAM treatment reported the virologic response at levels of 30% to 35%, another study reported as 67% [4, 10]. Both studies included HBeAg-negative patients. In this study, there were HBeAg-negative patients except for one patient, and the virologic response ratio was found to be within the ranges reported in the literature. An HBeAg-positive patient was found to develop HBeAg seroconversion. A study that made a five-year follow-up of LAM treatment reported HBeAg seroconversion after 0.2-14.7 (median=5.9) years [9]. HBeAg seroconversion duration in our patient could not be detected clearly as there were no follow-up tests during the study period. The European Association for the Study of the Liver (EASL) guideline recommends that LAM treatment could be ceased with HBeAg seroconversion, yet it also reports the recurrence risk [7]. Virologic response was obtained in our patient and the LAM treatment continued. HBsAg seroclearence was detected in 11.7% of patients who received long-term LAM treatment [4]. Studies report that HBsAg seroclearance is not always accompanied by seroconversion. Two patients in our study were also found to develop Anti-HBs with loss of HBsAg. One of these two was receiving immunosuppressive therapy due to renal transplantation. This initially HBV-DNA negative patient was started LAM treatment six years ago.

In our study, we had 9 cases receiving LAM prophylaxis (27.27%), which included five rheumatologic comorbidities, two renal transplant cases, one MM and one breast cancer patient. LAM prophylaxes were started without taking a liver biopsy, as mentioned in current guidelines. The duration of prophylaxis is not certain, but based on the recommendation indicating that it should continue at least 12 months after the cessation of immunosuppressive therapy, LAM prophylaxis is still continued in all patients [7]. The other patient who was detected to have HBsAg seroclearance and HBs seroconversion was under LAM treatment for the last 10 years. According to the EASL guidelines, HBsAg seroclearance was recommended to be an ideal point for ceasing the treatment regardless of the presence of HBs seroconversion. However, even if the treatment was ceased, watchful waiting was also recommended due to the HCC risk [7]. LAM treatment has not been ceased in this patient yet considering the disruptions to be experienced in watchful waiting under the pandemic conditions.

Compared to the last evaluation, we found an increase in the ratio of granular appearance in the USG imaging or the liver. Even if a response is received in the LAM treatment, risk factors for HCC development are known as older age, male gender, and cirrhotic changes in the liver. Although we had male patients and patients with liver cirrhosis in this study, it is pleasing that HCC was not detected in any USG imaging.

As reported in the literature, while the whole world is fighting the COVID-19 pandemic, difficulties are still experienced in the diagnostic evaluation and treatment of chronic diseases like cancer [11]. Infectious diseases specialists who perform the follow-up and treatment of CHB patients were among the top in the fight against the pandemic, which particularly contributed to the disruptions experienced in the follow-up of these patients. Especially patients who receive CHB treatment are recommended to have their biochemical tests done every 12 weeks [7]. In line with this, all patients in this study were found to have delays in their follow-ups during the study period. While our patients should have had eight visits in total within this period, they were found to have 1.94 (0.24) visits on average. Hence, the duration between the follow-ups was 13.81 (1.28) months on average. Similar to the studies conducted in the world and in our country, during the pandemic period, there was

a significant decrease in the number of biopsies and CHB patients having their outpatient follow-ups regularly [12, 13]. As this study shows, the patient who did not demonstrate a virologic response should have been evaluated in terms of treatment change. Unfortunately however, due to the pandemic, the results could not be evaluated, although the patient's HBV-DNA tests were requested.

Limitations

The strengths of this study are the duration length of LAM use and the continued treatment according to the guidelines, although the patients had HBeAg and HBsAg seroconversion. The limitations of the study are being a single center, retrospective cohort study with loss of data. Due to time interval, the study could cause the exclusion of patients in both bias who received or ceased LAM treatment. Further studies including all patients receiving LAM treatment due to CHB could demonstrate the efficiency of the LAM treatment better. Besides, there is a need for further studies to evaluate the effects of the pandemic on CHB patients.

Conclusion

In conclusion, watchful waiting is recommended even if serologic or virologic response is obtained with the LAM treatment, which was excluded from being the primary treatment option due to resistance in CHB. Since when the pandemic will end is unknown, test and treatment changes in CHB patients should be done before complications develop.

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