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Five-year results of oral antiviral therapy in HBeAg-negative chronic Hepatitis B

LIVER

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Original Article

ABSTRACT

Background/Aims: Several guidelines recommend the use of tenofovir or entecavir as the first-line treatment for hepatitis B due to the lower resistance rates of these drugs than lamivudine, although lamivudine may still be preferred because of its low adverse effect profile and cost. It is important to know which patients might benefit from lamivudine as the first-line treatment. We aimed to assess the success rates of lamivudine, entecavir, and tenofovir, as well as the resistance rates, frequencies of HBsAg clearance, and risk factors for lamivudine resistance.

Materials and Methods: A total of 191 patients with chronic HBeAg-negative hepatitis who were treated with lamivudine, entecavir, or tenofovir were included. Predictors of resistance to lamivudine were analyzed.

Results: The cumulative first-, second-, third-, fourth-, and fifth-year rates of virologic breakthrough during extended lamivudine therapy were 24%, 30%, 38%, 46%, and 54%, respectively. The rate of undetectable DNA at the 60th month of those who took lamivudine was 51%. Cox regression analysis revealed that positive HBV DNA at the sixth month (HR=15; 95% CI: [7.1–33], p=0.001), being aged 41 years or more (HR=3.4; 95% CI: [1.8–6.4], p=0.001), and baseline HBV DNA of 170,500 IU/mL or higher (HR=2.1; 95% CI: [1.2–3.7], p=0.01) were independently associated with the development of resistance to lamivudine.

Conclusion: In HBeAg-negative chronic hepatitis B, baseline serum hepatitis B virus DNA levels exceeding 170,500 IU/mL, partial virologic response in the sixth month, and age of 41 years or more were independent predictors for virologic breakthrough. Moreover, 2% of these patients cleared HBsAg.

Keywords: Antiviral agents, Hepatitis B, lamivudine

INTRODUCTION

Chronic hepatitis B is a chronic infectious disease that requires lifelong follow-up. It is estimated that globally, the number of people affected by chronic hepatitis B virus (HBV) infection is approximately 350 million (1,2). Clinical studies have shown that antiviral therapy can decrease the rate of hepatocellular carcinoma by reducing the progression of inflammation and fibrosis (3-5). Lamivudine was the first oral nucleoside analog approved for the treatment of chronic hepatitis B (6,7). Although its low cost is an important advantage, the potential risk of resistance against lamivudine over time is an important issue. Lower resistance rates against entecavir and the absence of any reported resistance against tenofovir, to date, are advantages of these two agents; however, treatment with these agents is associated with higher cost (8). Resistance against lamivudine over time causes several drawbacks, particularly because it is the most preferred drug for the treatment of HBV (9,10). It has been determined that resistance against lamivudine increases at a rate of 14 to 32% annually and reaches approximately 70% at the end of a five year period (11-13). Another disadvantage of lamivudine is that it may limit the use of some other nucleoside analogs in subsequent periods due to cross-resistance, which limits the success rates of medical treatment options (14). As a result, current guidelines suggest that the first step of treatment should be entecavir or tenofovir, which

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have higher resistance barriers (15,16). However, owing to its good clinical tolerability, its cost-effectiveness, and its advantageous safety profile in comparison with other drugs, some authors still claim that lamivudine should remain the preferred first-line treatment (17). In this retrospective study, we aimed to investigate lamivudine, entecavir, and tenofovir monotherapies on resistance rates, HBsAg clearance frequency, and risk factors for lamuvidine resistance.

MATERIALS AND METHODS

This retrospective study comprised adult patients with HBeAg negative chronic hepatitis B (CHB) who received long-term oral antiviral drug therapy between 2009 and 2014. Inclusion criteria were as follows: a positive test result of hepatitis B surface antigen and a negative HBeAg for 6 months or more, an ALT level that was more than double the normal range on two occasions, a HBV DNA level higher than 50 IU/mL within the last month before the onset of medical treatment, and histopathologic findings that showed a histologic activity index higher than 5 and a fibrosis score ≥2. Exclusion criteria were previous HBV treatment, positive serology for hepatitis C, D, or human immunodeficiency virus, autoimmune hepatitis, and previous liver transplantation. Follow-up at our center included routine clinical and laboratory examination and HBV-DNA levels, which were repeated every 6 months. Serum HBV-DNA levels were investigated using a quantitative polymerase chain reaction (PCR) assay (COBAS AmpliPrep Hepatitis B Virus (HBV) Test: HBV Monitor Test, Roche); the broad linear range of this assay according to the manufacturer is 20–1.7x10^8 IU/mL.

The treatment choice of the patients who were enrolled in this study was made according to the reimbursement rules of health insurance in our country, Turkey. Until 2014, the Turkish reimbursement guidelines for chronic hepatitis stated that patients who had hepatitis Be antigen (HBeAg) negative chronic hepatitis B with HBV-DNA levels between 2000 and 2,000,000 IU/mL could be treated with a nucleoside analog such as lamivudine. It was permitted to add tenofovir to lamuvidine in patients who had HBV DNA levels higher than 50 IU/mL after 6 months. On the other hand, patients who had HBV-DNA levels over 2,000,000 IU/mL were allowed to be treated with entecavir (ETV) or tenofovir (TFV).

Virologic response was accepted as undetectable serum HBV-DNA. Biochemical response was considered to be the decline of ALT below the normal limit (<40 IU/L). Virologic breakthrough was defined as the reappearance of detectable levels of HBV-DNA using PCR after a virologic response. Virologic remission was defined as ongoing virologic response without virologic breakthrough for 6 months or more during follow-up.

In our clinical practice, we do not change the oral antiviral therapy if HBV DNA levels are close to undetectable in patients with a partial response who had a marked DNA decrease at 6 months.

We compared patients with or without resistance to lamivudine in order to define risk factors for lamivudine resistance in this study population.

Liver histology

All patients underwent liver biopsy within 12 months of starting treatment. The histopathologic findings were noted as grade and stage in accordance with the Ishak classification system (18).

Statistical analysis

All data were analyzed using the SPSS statistical package version 21.0 (IBM Inc.; Chicago, IL, USA). Categorical data are presented with numbers and percentages. Continuous data are presented with mean±standard deviations or median (range) according to the distribution of the data. Fisher's exact or Chi-square test and Mann-Whitney test or Student's t-test were used to compare qualitative and quantitative data, respectively, when appropriate. Receiver operator characteristics (ROC) curves and Cox regression analyses were used to define risk factors for resistance to lamivudine. A two-tailed value of $p<0.05$ was accepted as statistically significant.

RESULTS

A total of 191 patients with HBeAg negative chronic hepatitis B infection were included in the study. The patients' demographic and baseline characteristics are shown in Table 1. Their mean age was 43.3±13.1 years (range, 18 to 77 years). The majority of the patients were men (66%). The mean DNA levels (range) for lamivudine, tenofovir, and entecavir were 257.750 IU/mL (range, 2700 to 1,850,000 IU/mL), 175.4x10^6 IU/mL (range, 1.7x10^6 to 170x10^6 IU/mL), and 178.5x10^6 IU/mL (range, 1.1x10^6 to 170x10^6 IU/mL), respectively. In 58% (110/191) of the patients, the initial medication was lamivudine. The rates of te-

Table 1. Demographic, clinical, and virologic features of the 191 patients

Mean age (years)		43.3±13.1
Sex (male/female)		66%/34%
HBeAg negative/positive		100%/0%
ALT (IU/L) (min–max)		82 (18–500)
AST (IU/L) (min–max)		60 (11–488)
HBV DNA levels (Baseline)	Lamivudine group (IU/mL)	257.750 IU/mL (2700–1,850,000)
	Tenofovir group (IU/mL)	175.4x10^6 IU/mL (1.7×10^6–170×10^6)
	Entecavir group (IU/mL)	178.5x10^6 IU/mL (1.1×10^6–170×10^6)
Initial medication percent (%) (Lamivudine/Entecavir/Tenofovir)		58%/25%/17%
HBsAg clearance %		2%
Follow-up (months)		43.4±17.8

AST: aspartate aminotransferase; ALT: alanine aminotransferase; HBV: hepatitis B virus

nofovir and entecavir use were 17% (33/191) and 25% (48/191), respectively. The median follow-up period under treatment was 43.4±17.8 months (range, 12 to 66 months).

In 3 (2%) of the 191 patients with sustained virologic response, HBsAg clearance was achieved after 18 months of treatment in 2 patients and 36 months in the other. After anti-HBs seroconversion, all three patients discontinued lamivudine, and none of the patients showed reactivation during a median post-treatment follow-up of 12 months. The cumulative rates of virologic breakthrough and the rate of the patients who remained on lamivudine therapy are shown in Figure 1. The rate of undetectable DNA at the 60th month of lamivudine was 51%.

Fifty-four percent of the patients (59/110) showed virologic breakthrough during the 43.4±17.8-month follow-up period (Figure 2). Tenofovir was added to lamuvidine after the detection of virologic breakthrough. The median duration of combined treatment of tenofovir plus lamivudine in these patients was 12 months (range, 6 to 18 months). Sustained virologic response rates were 44%, 86%, 100%, and 94% under entecavir, and 22%, 72%, 100%, and 100% with tenofovir at the end of 6, 12, 18, and 60 months, respectively. The virologic breakthrough rate was 4% throughout the follow-up period of 39±17 months under entecavir treatment. No resistance was determined among the patients who were using tenofovir.

Risk factors for virologic breakthrough

Patients with resistance to lamivudine were older (48.1±13.3 years vs. 34.1±8.2 years, p<0.001) and had higher baseline HBV DNA levels compared with those without resistance to lamivudine (246,000 IU/mL [range, 2700 to 737,000 IU/mL] vs. 87,560 IU/mL [10,000 to 1,850,000 IU/mL], p<0.001). However, baseline AST or ALT levels were similar in patients with resistance to lamivudine and in those without resistance. ROC curve analyses revealed an age of 41 or older (AUC 0.82; 95% CI: [0.73-0.91] p<0.001; sensitivity 78% and specificity 82.4%) and initial HBV DNA level of 170,500 IU/mL or higher (AUC 0.8; 95% CI: [0.72–0.88] p<0.001; sensitivity 71% and specificity 78.4%) (Figure 3, 4).

Cox regression analysis (covariates: sex, partial virologic response in the sixth month, age of 41 years or more, and a baseline HBV DNA of 170,500 IU/mL or higher) revealed that an age of more than 41 years (HR=3.4; 95% CI: [1.8–6.4], p= 0.001) and baseline HBV DNA levels higher than 170,500 IU/mL (HR=2.1; 95% CI: [1.2–3.7], p=0.01) were independently associated with the development of resistance to lamivudine.

DISCUSSION

In this study, we investigated remission and resistance rates and HBsAg clearance over a 5-year period in 191 patients who took lamivudine, entecavir or tenofovir. We also compared patients with or without resistance to lamivudine in order to define risk factors for lamivudine resistance in this study population. We used lamivudine therapy in the majority of these

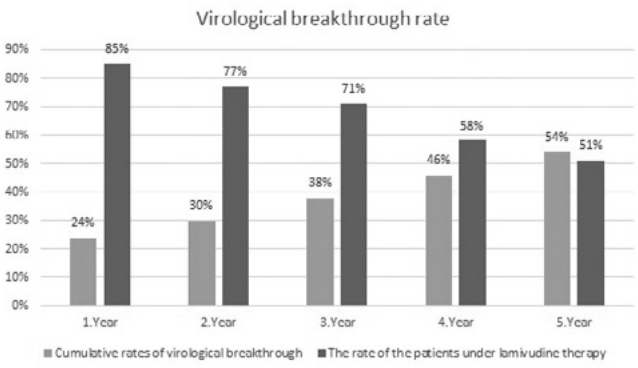

Figure 1. Rates of virologic breakthrough and lamivudine use

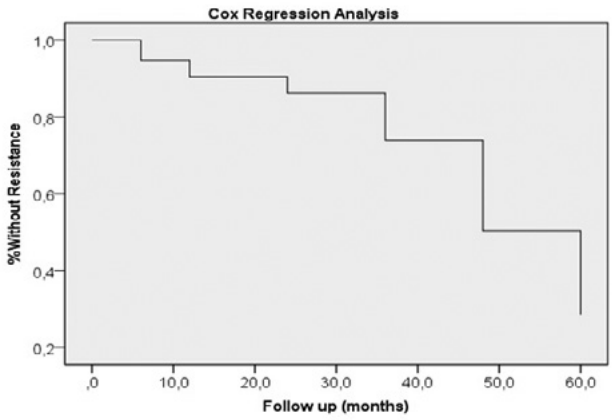

Figure 2. Survival plot showing the rate of patients without resistance to lamivudine

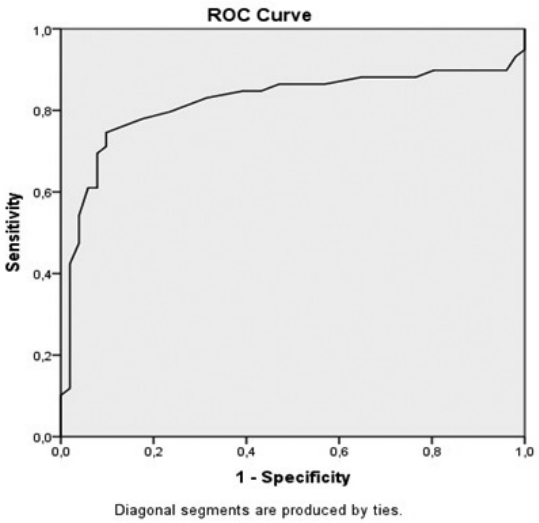

Figure 3. ROC curve analysis for resistance to lamivudine according to age

patients because of health reimbursement rules. Among the patients who were undergoing lamivudine therapy, HBV DNA suppression was observed in more than half at the end of the first 6 months and in the majority at the end of the first year. At the end of the fifth year, virologic remission was achieved in half of the patients. Similarly, at the end of the fifth year, half of the patients were still under lamivudine therapy. During a me-

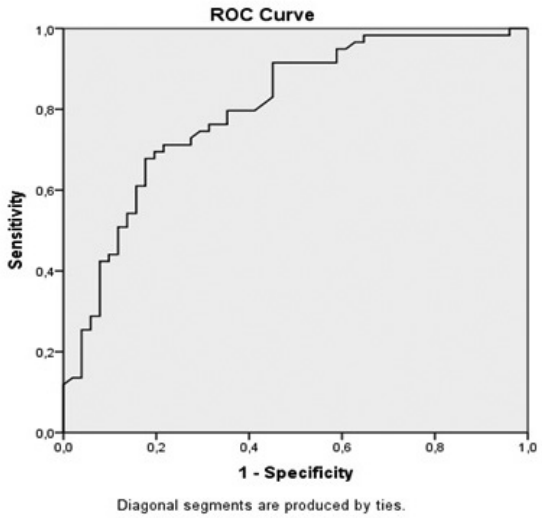

Figure 4. ROC curve analysis for resistance to lamivudine according to baseline HBV DNA level

dian period of 43 months under lamivudine therapy, resistance against lamivudine developed in nearly half of the patients. Older age and higher baseline HBV DNA were associated with the development of resistance to lamivudine in the follow-up. Furthermore, partial virologic response in the sixth month was a strong and independent predictor of development of resistance to lamivudine. Although patients under entecavir had similar rates of HBV DNA suppression at 6 months and 1 year compared with patients under lamivudine, this rate was significantly better for entecavir in the following years. Even though patients treated with tenofovir had a lower rate of HBV DNA suppression at 6 months than those under lamivudine, this rate was similar at the end of the first year, and significantly better in subsequent years. HBsAg clearance was observed in only 3 patients who took lamivudine.

Lamivudine has recently caused concerns because it is the first-choice agent but has relatively high resistance rates. However, lamivudine still remains the most preferred agent by health reimbursement institutions in some countries, owing to its low rates of adverse effects and its low cost compared with other antiviral agents (4,17). Considering our data, lamivudine therapy may still be preferred as the first-line treatment, at least in selected cases, because half of the patients who were under lamivudine had resistance throughout the 3.5-year follow-up.

Concerning studies in which patients with HBeAg negative chronic hepatitis B were under antiviral therapy, different rates have been determined regarding HBV-DNA suppression, resistance and virologic breakthrough. Lamivudine is associated with rapid biochemical and virologic response rates in the short term. However, regression and improvement of liver fibrosis requires successful long-term therapy (4,19-22). In the study of Fasano et al. (17), 636 patients with HBeAg negative chronic hepatitis B who were treated with lamivudine for 5 years were assessed. Throughout a treatment period of 5 years, 70% of the patients developed resistance to lamivudine; HBV DNA remained suppressed in 67% of the 191 patients. These patients remained in remission after 5 years during a median follow-up period of 36 months, and virologic breakthrough associated with resistance was reported to be 33% in a median period of 15 months (17). George et al. (23) reported HBV DNA suppression rates in 209 patients with HBeAg-negative chronic hepatitis B as 73.2% at the end of the first year, 52.3% at the end of 2 years, 40% at the end of 3 years, and 34% at the end of 4 years, whereas failure rates were approximately 46% within this period. In another study, Vito et al. reported HBV DNA suppression rates that were 88.6% in the first year, 63% in the second year, 48% in the third year, and 39% in the fourth year in 616 patients with HBeAg negative chronic hepatitis B; the virologic failure rate was 33% under lamivudine (13).

In our study, HBV DNA suppression was observed in more than half of the patients after six months and in most of the patients at the end of the first year. This rate was slightly higher than the results observed in the literature. At the end of the fifth year, HBV DNA suppression was achieved in half of the patients. However, in our study, independent predictors of resistance to lamivudine were partial virologic response at 6 months, being aged 41 years or more, and baseline HBV DNA levels of 170,500 IU/mL or higher. Sex and baseline transaminase levels were not associated with the development of resistance to lamivudine. The utility of these factors when deciding on the first-line treatment agent needs to be validated in further prospective studies.

Lamivudine is a cost-effective treatment for chronic HBV (24,25). Although newer agents such as entecavir and tenofovir appear to be more effective, the increased cost is an important problem. In one meta-analysis on cost-effectiveness, 3 of 6 studies indicated that lamivudine seemed to be more cost-effective (26). The selection of one of these agents completely depends on the available health care budget and willingness to pay. For developing countries where patients cannot afford costly drugs, it appears rational to start with lamivudine and switch to adefovir or entecavir after the detection of resistance (27).

Our study has several limitations, which include the retrospective design, the absence of control groups for comparison, and the lack of genetic analyses that could have more accurately demonstrated resistance rates.

In conclusion, in this retrospective study of patients with chronic hepatitis B who were under lamivudine, entecavir, or tenofovir treatment, a high proportion of those on lamivudine had stable clinical courses for extended periods. Higher baseline HBV DNA levels, older age, and a partial virologic response in the sixth month were predictors of resistance to lamivudine. Considering cost-effectiveness, we believe that lamivudine can be chosen as the first-line treatment, at least in selected cases. However, prospective studies are needed to determine which patients would benefit from long-term lamivudine treatment and which patients need to use other agents at the first step.

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