Changes in the clinical characteristics of chronic hepatitis B patients at the initiation of treatment over a 15-year period

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Abstract

Background and Aim: This study aimed to evaluate the changes in the clinical characteristics of chronic Hepatitis B (CHB) patients at the initiation of treatment over a 15-year period.

Materials and Methods: The study included 659 treatment-naive CHB patients who started receiving nucleos(t)ide analogs between January 2006 and December 2020. The patients included in the study were divided into three groups of five years each, according to the start date of treatment.

Results: The mean age was 46.2±14.5 years and 445 (67.5%) were male. Two hundred and five (31.1%) patients had cirrhosis. Hepatocellular carcinoma (HCC) developed in forty-one patients (6.2%). Compared to patients in Group 1, Group 2 were younger and had lower compensated cirrhosis, HCC and ascites, had higher Child A cirrhosis (all p<0.05). Cirrhosis and esophageal varices were higher in patients in Group 3 compared to patients in Group 2 (all p<0.05). Entecavir or tenofovir use increased from 66.5% in Group 1 to 99.2% in Group 3 (p<0.05).

Conclusion: The mean age at initiation of treatment for CHB patients increased. The patients had less cirrhosis. In the last 5 years, almost all patients were treated with entecavir or tenofovir.

Keywords: Clinical characteristics; chronic hepatitis B; initiation of treatment.

Introduction

Hepatitis B virus (HBV) infection remains an important public health problem despite advances in treatment and vaccination. It is estimated that one-third of the world’s population is infected with HBV and approximately 240 million patients have chronic hepatitis B (CHB) infection. Although hepatic complications do not develop in the majority of CHB infections, serious hepatic diseases such as cirrhosis and hepatocellular carcinoma may develop in 15-40% of the patients. [1] CHB infection is also the most common cause of liver transplantation in Turkey.[2] The aim of treatment in CHB infection is to improve the quality of life and survival of patients. Cirrhosis, decompensated cirrhosis, end-stage liver disease, hepatocellular carcinoma and death are prevented with appropriate treatment of the disease. Treatment also contributes to the prevention of transmission by suppressing HBV replication. Treatment decision in CHB infection is based on serum HBV-DNA level, serum ALT level and severity of liver disease.[3] Immediate antiviral therapy is recommended for patients with decompensated cirrhosis with detectable serum HBV-DNA. Clinical improvement can be achieved in these patients by controlling viral replication. However, antiviral therapy is not sufficient to save all patients with decompensated cirrhosis, and liver transplantation may be required.[4] The relative risk of developing HCC in CHB patients is 100-223 times higher than in the normal population.[5] In conclusion, it is extremely important to initiate appropriate treatment as soon as possible before the development of chronic liver disease, cirrhosis and HCC in CHB infection.

In the present study, we aimed to evaluate the clinical characteristics of CHB patients at the initiation of treatment over a 15-years period.

Materials and Methods

In this study, electronic records of 659 patients with chronic HBV infection who started receiving nucleos(t)ide analogs in the Gastroenterology Outpatient Clinic of our hospital between January 2006 and December 2020 were retrospectively reviewed. The study included nucleos(t)ide analogs naive CHB patients with or without cirrhosis. Patients were excluded if they were 1) <18 years old at admission, 2) had received nucleos(t)ide analogs treatment, 3) were co-infected with hepatitis C, hepatitis D, or human immune deficiency viruses, or 4) had a history of liver transplantation prior to therapy. Laboratory test results including HBsAg, serum HBV DNA levels, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), albumin, bilirubin and AFP levels, prothrombin time (PT), international normalized ratio (INR), and complete blood count at the start of therapy were recorded. Liver biopsy results, if available and results of imaging studies [USG, triphasic computed tomography (CT) and dynamic magnetic resonance imaging (MRI)] were recorded. CHB was diagnosed if patients were HBsAg positive for more than 6 months. Cirrhosis was diagnosed if patients had stage 5-6 fibrosis[6] on liver biopsy, and/or nodularity and irregularity on the liver surface, elevated portal vein diameter or splenomegaly (with thrombocytopenia) on imaging studies, and/or esophageal gastric varices on upper gastrointestinal endoscopy. Decompensated cirrhosis was diag-
nosed if there was a history of variceal bleeding, hepatic encephalopathy or ascites. Patients whose histological, radiological and laboratory test results were not compatible with cirrhosis were defined as noncirrhotic. [8] Patients started receiving nucleos(t)ide analogs based on their serum HBV DNA levels, serum ALT levels and severity of liver disease according to the regulation of the Turkish Social Security Institution. Initiation criteria for therapy were as follows: 1) HBV DNA ≥2,000 IU/mL and histological activity index ≥6 or fibrosis ≥2 regardless of serum ALT levels and HBeAg status in non-cirrhotic patients, 2) positive serum HBV DNA independent of serum HBV DNA and ALT levels, and HBeAg positivity in patients with histologically, radiologically and endoscopically proven cirrhosis. By the year 2010, if HBV DNA ≥20,000 IU/mL and serum ALT levels ≥x upper limit of normal for ≥6 months therapy was initiated without the need for liver biopsy in both HBeAg positive and negative patients. [8] The diagnosis of HCC was made according to the guidelines. [8]

The patients included in the study were divided into three groups of five years each, according to the date of initiation of treatment. Those who started treatment between 01.01.2006-31.12.2010 were defined as Group 1, between 01.01.2011-31.12.2015 as Group 2, and between 01.01.2016-31.12.2020 as Group 3. The differences between these three groups were compared with statistical methods.

### Statistical Analyses

Statistical analyses were performed using SPSS statistical software version 23.0 (IBM® SPSS®, Chicago, IL). Variables were characterized using mean, maximum, and minimum values, while percentage values were used for qualitative variables. Normal distribution was confirmed using tests such as the Kolmogorov-Smirnov test. Normal distributions were reported as mean±SD. Student’s t-test was used for comparisons between groups. Pearson’s chi-square test was used in the analysis of qualitative variables, and Fisher’s exact test was used if the group was small. Non-parametric continuous variables were recorded as median and interval distributions, and Kruskal-Wallis one-way ANOVA was used to compare non-parametric variables within three groups, and Mann-Whitney U tests were used for pairwise group comparison. A p<0.05 was considered statistically significant. In this study, it was also accepted that there was a tendency towards significance if the p-value was between 0.05 and 0.099. The Bonferroni method was used to adjust multiple group comparisons for continuous variables. However, if there is a situation where the distributions are not homogeneous (without the Homogeneity Test of Variances), the Tamhane test was used. Since three groups were formed, significance was accepted as 0.05/((n*(n-1))/2) in the multi-group comparison (0.05/(3*(3-1)/2) = 0.017). Therefore, p<0.017 was considered significant in posthoc tests (both in bonferroni and Tamhane).

The study was carried out in accordance with the Helsinki Declaration and approved by the local ethics committee (approval no: 06.07.2021/E-62977267-771). Informed consent was not obtained due to the retrospective design of the study.

### Results

The study included 659 patients. The mean age was 46.2±14.5 years and 445 (67.5%) were male. One hundred and seventy-seven were positive for HBeAg (26.9%). Two hundred and five (31.1%) patients had cirrhosis and seventy-three (35.6%) of patients with cirrhosis were decompenated. HCC developed in forty-one patients (6.2%). Demographic, clinical and laboratory findings of the patients are shown in Table 1.

| Table 1. Demographic, clinical and laboratory findings of the patients |
|-------------------------|-------|-----------------|
| n                      | %     |
| Age (years, mean±SD)   | 46.2±14.5 |
| Date of treatment initiation |       |
| Group 1                | 182   | 27.6 |
| Group 2                | 217   | 32.9 |
| Group 3                | 260   | 39.5 |
| Gender                 |       |       |
| Female                 | 214   | 32.5 |
| Male                   | 445   | 67.5 |
| Cirrhosis              |       |       |
| Yes                    | 205   | 31.1 |
| No                     | 454   | 68.9 |
| HBeAg                  |       |       |
| Yes                    | 124   | 18.8 |
| No                     | 535   | 81.2 |
| Biopsy                 |       |       |
| Yes                    | 81    | 12.3 |
| No                     | 578   | 87.7 |
| Cirrhosis subtype*     |       |       |
| Companse               | 132   | 64.4 |
| Decompansese           | 73    | 35.6 |
| Child classification*  |       |       |
| A                      | 134   | 65.4 |
| B                      | 51    | 24.9 |
| C                      | 20    | 9.8  |
| HCC                    |       |       |
| Yes                    | 41    | 6.2  |
| No                     | 618   | 93.8 |
| Treatment agent        |       |       |
| Lamivudine             | 81    | 12.3 |
| Entekavir              | 261   | 39.6 |
| Tenofovir              | 303   | 46.0 |
| Telbuvidine            | 14    | 2.1  |
| HBeAg                  |       |       |
| Negative               | 482   | 73.1 |
| Positive               | 177   | 26.9 |
| Ascites                |       |       |
| Yes                    | 62    | 9.4  |
| No                     | 597   | 90.6 |
| Esophageal varices#    |       |       |
| Yes                    | 98    | 14.9 |
| No                     | 561   | 85.1 |
| HBV-DNA (x10^3 IU/ml, mean±SD) | 36.3±141.8 |
| BUN (mg/dl, mean±SD)   | 14.2±6.0 |
| Creatinine (mg/dl, mean±SD) | 0.82±0.37 |
| AST (IU/L, mean±SD)    | 92.3±191.4 |
| ALT (IU/L, mean±SD)    | 133.3±271.6 |
| ALP (IU/L, mean±SD)    | 94.6±68.0 |
| GGT (IU/L, mean±SD)    | 59.1±74.7 |
| Protein (gr/dL, mean±SD) | 7.3±3.1 |
| Albumin (gr/dl, mean±SD) | 3.8±0.6 |
| Bilirubin (mg/dl, mean±SD) | 1.17±2.13 |
| AFP (ng/mL, mean±SD)   | 149.8±1502.7 |
| Prothrombin Time (second, mean±SD) | 14.0±2.6 |
| INR (mean±SD)          | 1.13±0.19 |
| WBC (mm³, mean±SD)     | 6377.9±2513.7 |
| Hemoglobin (mg/dl, mean±SD) | 13.8±1.8 |
| Platelet (x10^11/mm³, mean±SD) | 181.9±68.7 |

*: 205 patients with cirrhosis; #: 5 patients with esophageal varices had bleeding; SD: Standard deviation; Group 1: 01.01.2006-31.12.2010; Group 2: 01.01.2011-31.12.2015; Group 3: 01.01.2016-31.12.2020; HCC: Hepatocellular carcinoma; BUN: Blood urea nitrogen; AST: Aspartate transferase; ALT: Alanine transferase; GGT: Gamma-glutamyl transpeptidase; ALP: Alkaline phosphatase; AFP: Alpha fetoprotein; PT INR: International normalized ratio; WBC: White blood cells.
There was no difference between the groups in terms of gender, HBeAg status and the presence of varices (p=0.105, p=0.145 and p=0.116, respectively). In comparison to patients in Group 1, Group 2 were younger, had lower decompensated cirrhosis, HCC and ascites, higher Child A cirrhosis (all p<0.05). Cirrhosis and esophageal varices were higher in patients in Group 3 compared to patients in Group 2 (all p<0.05). There was a significant difference between the groups in the treatment agent and lamivudine treatment was not started in any patient in Group 3. The comparison of the variables between Group 1, Group 2, and Group 3 are shown in Table 2.

There was no significant difference between the groups in laboratory values of HBV-DNA, creatinine, AST, ALT, total protein, albumin, PT, INR, and hemoglobin (all p<0.05). Comparison of the laboratory variables between groups is shown in Table 3.

**Discussion**

In the present study, we evaluated the clinical characteristics of CHB patients at the initiation of treatment over a 15-year period. In our cohort, the mean age of patients increased over the years and the incidence of cirrhosis decreased. Entecavir or tenofovir was used in 99.2% of the patients in the last 5-year period.

The epidemiology of CHB infection has changed significantly with universal newborn vaccination. In a systematic review published by the World Health Organization in 2012, it was shown that the prevalence of CHB decreased in many parts of the world between 1990 and 2005. It has been observed that the prevalence of HBsAg positivity has decreased over the years in Turkey as well as in the world. In the present study, the mean age of the patients who started treatment in Group 2 increased significantly compared to Group 1, while Group 2 and Group 3 were found to be similar. This may be due to the decrease in the incidence of HBV infection in young people as a result of vaccination. In addition, HBsAg and Anti-HCV have been added to mandatory premarital tests since 2002 in our country, and patients are diagnosed at a younger age.

### Table 2. Comparison of groups formed according to treatment initiation date

|                       | Group 1 (n=182) | Group 2 (n=217) | Group 3 (n=260) | p    | p¹   | p²  |
|-----------------------|-----------------|-----------------|-----------------|------|------|-----|
| Age (years, mean±SD)  | 43.5±14.2       | 47.2±14.7       | 47.4±14.4       | 0.02 | 0.018| 0.939|
| Gender                |                 |                 |                 | 0.105| 0.871| 0.053|
| Female                | 64 (35.2)       | 78 (35.9)       | 72 (27.7)       |      |     |     |
| Male                  | 118 (64.8)      | 139 (64.1)      | 188 (72.3)      |      |     |     |
| Cirrhosis             | 61 (33.5)       | 77 (35.5)       | 67 (25.8)       | 0.053| 0.681| 0.021|
| Cirrhosis subtype*    |                 |                 |                 | 0.001| <0.001| 0.658|
| Compensated           | 51 (83.6)       | 42 (54.5)       | 39 (58.2)       |      |     |     |
| Decompensated         | 10 (16.4)       | 35 (45.5)       | 28 (41.8)       |      |     |     |
| Child classification* |                 |                 |                 | 0.004| 0.001| 0.677|
| A                     | 51 (83.6)       | 42 (54.5)       | 41 (61.2)       |      |     |     |
| B                     | 5 (8.2)         | 27 (35.1)       | 19 (28.1)       | 0.053| 0.681| 0.021|
| C                     | 5 (8.2)         | 8 (10.4)        | 7 (10.4)        |      |     |     |
| HCC                   |                 |                 |                 | 0.061| 0.018| 0.572|
| Yes                   | 5 (2.7)         | 18 (8.3)        | 18 (6.9)        |      |     |     |
| No                    | 177 (97.3)      | 199 (91.7)      | 242 (93.1)      |      |     |     |
| Treatment agent       |                 |                 |                 | <0.001| <0.001| <0.001|
| Lamivudine            | 61 (33.5)       | 20 (9.2)        | 0 (0)           |      |     |     |
| Entekavir             | 83 (45.6)       | 93 (42.9)       | 85 (32.7)       |      |     |     |
| Tenofovir             | 38 (20.9)       | 92 (42.4)       | 173 (66.5)      |      |     |     |
| Telbuvidine           | 0 (0)           | 12 (5.5)        | 2 (0)           |      |     |     |
| HBeAg                 |                 |                 |                 | 0.145| 0.796| 0.114|
| Negative              | 127 (69.8)      | 154 (71.0)      | 201 (77.3)      |      |     |     |
| Positive              | 55 (30.2)       | 63 (29.0)       | 59 (22.7)       |      |     |     |
| Ascites               |                 |                 |                 | 0.060| 0.022| 0.153|
| Yes                   | 11 (6.0)        | 28 (12.9)       | 23 (8.8)        |      |     |     |
| No                    | 171 (94.0)      | 189 (87.1)      | 237 (91.2)      |      |     |     |
| Esophageal varices*   |                 |                 |                 | 0.116| 0.167| 0.047|
| Yes                   | 25 (13.7)       | 41 (18.9)       | 32 (12.3)       |      |     |     |
| No                    | 157 (86.3)      | 176 (81.1)      | 228 (87.7)      |      |     |     |

¹: Group 1 versus Group 2; ²: Group 2 versus Group 3; *: 205 patients with cirrhosis; #: 5 patients with esophageal varices had bleeding; Group 1: 01.01.2006-31.12.2010; Group 2: 01.01.2011-31.12.2015; Group 3: 01.01.2016-31.12.2020; HCC: Hepatocellular carcinoma.
In a study conducted in Asia, a decrease in the incidence of chronic liver disease and HCC was observed after the start of the vaccination program.[11] However, the incidence of patients with decompensated cirrhosis increased, while compensated cirrhosis decreased. Due to this increase, the incidence of Child C cirrhosis patients increased significantly. Also, ascites and esophageal varices were increased in Group 2 patients. In comparison to patients in Group 2, Group 1 had higher and Group 3 had similar HCC. The reason for this result is that our hospital is a tertiary referral center.

Currently, CHB guidelines recommend the use of entecavir and tenofovir as first-line therapy.[12,13] In Turkey, Entecavir has been used since 2007 and Tenofovir has been used since 2008. Entecavir or tenofovir use increased from 66.5% in Group 1 to 99.2% in Group 3. In our cohort, no patient in Group 3 was started on lamivudine.

The present study has also some shortcomings. First, the study was retrospective and conducted in a single center. Second, the study was carried out in a tertiary referral center, and the prevalence of cirrhosis and HCC in our patient cohort was 31.1% and 6.2%, respectively.

In conclusion, the mean age at initiation of treatment for CHB patients increased. In the last 5 years period, almost all patients were treated with entecavir or tenofovir.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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