

# 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-years 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 decompensated 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. [1] 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. [3] The relative risk of developing HCC in CHB patients is 100-223 times higher than in the normal population. [4] 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 HBeAg, 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 the patients were HBsAg positive for more than 6 months. Cirrhosis was diagnosed if patients had stage 5-6 fibrosis [5] 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 esophago-gastric varices on upper gastrointestinal endoscopy. Decompensated cirrhosis was diag-

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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.<sup>[6]</sup> 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  $\geq 2,000$  IU/mL and histological activity index  $\geq 6$  or fibrosis  $\geq 2$  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  $\geq 20,000$  IU/mL and serum ALT levels  $\geq 2$  x upper limit of normal for  $\geq 6$  months therapy was initiated without the need for liver biopsy in both HBeAg positive and negative patients.<sup>[7]</sup> The diagnosis of HCC was made according to the guidelines.<sup>[8]</sup>

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. Whether the distribution was normal or not was determined by 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 decompensated. 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	205	31.1
Clinical	124	18.8
Biopsy	81	12.3
Cirrhosis subtype*		
Compense	132	64.4
Decompense	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		
Lamuvidine	81	12.3
Entekavir	261	39.6
Tenofovir	303	46.0
Telbuvidine	14	2.1
HBeAg		
Negative	482	73.1
Pozitive	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 <sup>6</sup> 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	
Billirubin (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 (/mm <sup>3</sup> , mean±SD)	6377.9±2513.7	
Hemoglobine (mg/dl, mean±SD)	13.8±1.8	
Platelet (x10 <sup>3</sup> /mm <sup>3</sup> , 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.

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

	Group 1 (n=182)		Group 2 (n=217)		Group 3 (n=260)		p	p <sup>1</sup>	p <sup>2</sup>
	n	%	n	%	n	%			
Age (years, mean±SD)	43.5±14.2		47.2±14.7		47.4±14.4		<b>0.02</b>	<b>0.018</b>	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	<b>0.021</b>
Cirrhosis subtype*							<b>0.001</b>	<b>&lt;0.001</b>	0.658
Compensated	51	83.6	42	54.5	39	58.2			
Decompensated	10	16.4	35	45.5	28	41.8			
Child classification*							<b>0.004</b>	<b>0.001</b>	0.677
A	51	83.6	42	54.5	41	61.2			
B	5	8.2	27	35.1	19	28.4			
C	5	8.2	8	10.4	7	10.4			
HCC							0.061	<b>0.018</b>	0.572
Yes	5	2.7	18	8.3	18	6.9			
No	177	97.3	199	91.7	242	93.1			
Treatment agent							<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Lamivudine	61	33.5	20	9.2	0	0			
Entecavir	83	45.6	93	42.9	85	32.7			
Tenofovir	38	20.9	92	42.4	173	66.5			
Telbivudine	0	0	12	5.5	2	0.8			
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	<b>0.022</b>	0.153
Yes	11	6.0	28	12.9	23	8.8			
No	171	94.0	189	87.1	237	91.2			
Esophageal varices <sup>#</sup>							0.116	0.167	<b>0.047</b>
Yes	25	13.7	41	18.9	32	12.3			
No	157	86.3	176	81.1	228	87.7			

<sup>1</sup>p: Group 1 versus Group 2; <sup>2</sup>p: 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.

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.<sup>[9]</sup> It has been observed that the prevalence of HBsAg positivity has decreased over the years in Turkey as well as in the world.<sup>[10]</sup> 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 3.** Comparison of the laboratory values of the groups formed according to the treatment initiation date

	Grup 1	Grup 2	Grup 3	p*	p <sup>1</sup>	p <sup>2</sup>	p <sup>3</sup>
HBV-DNA (x10 <sup>6</sup> IU/ml, mean±SD)	58.1±227.7	32.0±63.7	24.5±141.8	<0.001	0.201 <sup>#</sup>	0.043 <sup>#</sup>	1.000 <sup>#</sup>
BUN (mg/dl, mean±SD)	14.7±7.3	13.9±5.2	14.2±5.7	0.764	0.689 <sup>#</sup>	1.000 <sup>#</sup>	1.000 <sup>#</sup>
Creatinine (mg/dl, mean±SD)	0.89±0.67	0.78±0.14	0.81±0.15	0.001	0.087 <sup>α</sup>	0.269 <sup>α</sup>	0.155 <sup>α</sup>
AST (IU/L, mean±SD)	89.8±143.4	88.4±153.9	97.4±242.7	0.009	1.000 <sup>#</sup>	1.000 <sup>#</sup>	1.000 <sup>#</sup>
ALT (IU/L, mean±SD)	130.6±168.6	117.4±161.1	148.5±381.4	0.001	1.000 <sup>#</sup>	1.000 <sup>#</sup>	0.641 <sup>#</sup>
ALP (IU/L, mean±SD)	93.7±40.8	95.5±84.0	94.4±68.8	0.672	1.000 <sup>#</sup>	1.000 <sup>#</sup>	1.000 <sup>#</sup>
GGT (IU/L, mean±SD)	56.0±71.4	65.4±91.3	55.9±60.0	0.801	0.641 <sup>#</sup>	1.000 <sup>#</sup>	0.506 <sup>#</sup>
Protein (gr/dL, mean±SD)	7.3±0.6	7.1±0.6	7.5±4.8	0.046	1.000 <sup>#</sup>	1.000 <sup>#</sup>	0.690 <sup>#</sup>
Albumin (gr/dL, mean±SD)	4.0±0.5	3.6±0.5	3.9±0.6	<0.001	<0.001 <sup>α</sup>	0.329 <sup>α</sup>	<0.001 <sup>α</sup>
Billirubin (mg/dl, mean±SD)	1.0±1.4	1.2±2.7	1.1±1.9	0.962	1.000 <sup>#</sup>	1.000 <sup>#</sup>	1.000 <sup>#</sup>
AFP (ng/mL, mean±SD)	10.2±24.0	318.8±2200.8	111.9±1318.0	0.171	0.153 <sup>#</sup>	1.000 <sup>#</sup>	0.447 <sup>#</sup>
Prothrombin Time (second, mean±SD)	13.4±2.2	13.1±2.1	14.9±2.6	<0.001	0.740 <sup>α</sup>	<0.001 <sup>α</sup>	<0.001 <sup>α</sup>
INR (mean±SD)	1.09±0.15	1.12±0.19	1.15±0.21	0.001	0.299 <sup>α</sup>	0.003 <sup>α</sup>	0.272 <sup>α</sup>
WBC (/mm <sup>3</sup> , mean±SD)	6179.7±1895.6	6408.1±3397.6	6491.4±1968	0.404	1.000 <sup>#</sup>	0.600 <sup>#</sup>	1.000 <sup>#</sup>
Hemoglobine (mg/dl, mean±SD)	14.1±1.9	13.5±1.8	13.8±1.6	0.002	0.004 <sup>α</sup>	0.475 <sup>α</sup>	0.058 <sup>α</sup>
Platelet (x10 <sup>3</sup> /mm <sup>3</sup> , mean±SD)	182.4±72.1	175.7±69.8	186.8±65.1	0.375	1.000 <sup>#</sup>	1.000 <sup>#</sup>	0.238 <sup>#</sup>

\*: Kruskal-Wallis one way ANOVA; <sup>1</sup>p: Group 1 vs Group 2; <sup>2</sup>p: Group 1 vs Group 3; <sup>3</sup>p: Group 2 vs Group 3; #: Bonfferoni adjusted posthoc analyses; α: Tamhane adjusted posthoc analyses; 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; BUN: Blood urea nitrogen; AST: Aspartate transferase; ALT: Alanine transferase; GGT: Gamma-glutamyl transpeptidase; ALP: Alkaline phosphatase; AFP: Alpha-fetoprotein; INR: International normalized ratio; WBC: White blood cells.

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.<sup>[11]</sup> 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.<sup>[11,12,13]</sup> 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. The patients had less cirrhosis. In the last 5 years period, almost all patients were treated with entecavir or tenofovir.

**Ethics Committee Approval:** The Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 06.07.202, number: E-62977267-771).

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

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## References

- Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016;10(1):1-98.
- Akarsu M. Liver transplantation in Turkey: the importance of experience. *Turk J Gastroenterol* 2018;29(6):629-630.
- Liaw YF, Sheen IS, Lee CM, Akarca US, Papatheodoridis GV, Suet-Hing WF, et al. Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. *Hepatology* 2011;53(1):62-72.
- Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22,707 men in Taiwan. *Lancet* 1981;2(8256):1129-1133.
- Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995;22(6):696-699.
- European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;69(2):406-460.
- Sosyal Güvenlik Kurumu Sağlık Uygulama Tebliğinde Değişiklik Yapılmasına Dair Tebliğ. Available at: <https://www.resmigazete.gov.tr/eskiler/2020/06/20200616M1-1.pdf>. Accessed on Jun 16, 2021.
- Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018;68(2):723-750.
- Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine* 2012;30(12):2212-2219.

10. Tosun S. The changing viral hepatitis epidemiology in our country. *ANKEM Derg* 2013;27(Suppl 2):128-134. (Turkish)
11. Chiang CJ, Yang YW, You SL, Lai MS, Chen CJ. Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. *JAMA* 2013;310(9):974-976.
12. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017;67(2):370-398.
13. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018;67(4):1560-1599.