Research Article

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HCC and HBeAg (+) chronic hepatitis B infection

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Clinical follow-up of patients with HBeAg positive chronic hepatitis B infection: A long-term observational study

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Abstract

Background and Aim: We aimed to analyze the demographic, laboratory, and clinical characteristics of patients with HBeAg positive chronic hepatitis B infection in tertiary care centers in Istanbul.

Materials and Methods: We conducted an observational cohort with ≥18-year-old patients with HBeAg positive chronic hepatitis B infection, who were followed up in three tertiary care centers in Istanbul between January 2000 and August 2018, were evaluated by reviewing electronic and recorded files. The Ethical Committee of Istanbul Medipol University approved this study (Protocol no: 10840098-604.01.01-E.44136). During the polyclinic interview, consent was obtained from patients for analysis and publication.

Results: The mean age of the 64 patients was 30 (range 18-39) years, and 50% (32) of them were males. The mean follow-up period of the patients was 67 (18-180) months. Twenty-four patients were treated with at least one antiviral in their follow-up, and only 2 (3.1%) of these patients developed HBeAg seroconversion without antiviral treatment. HBeAg (+) chronic hepatitis B developed in 4 of the patients after the immune-active period. None of the patients and first-degree relatives had hepatocellular carcinoma (HCC).

Conclusion: The rationality of antiviral treatment and HCC development risk in these patients still remains elusive.

Keywords: Hepatitis B; hepatitis B e antigens; hepatocellular carcinoma.

Introduction

Hepatitis B virus (HBV) does not have a cytopathic effect.[1] The immune system of the host is the main factor in the progression of the disease.[2] Immature immune system and virus interaction lead to a tolerogenic condition in fetal, neonatal, or early childhood period as the first step of the natural course of HBeAg positive chronic hepatitis B infection. HBeAg positive chronic hepatitis B infection is characterized by high HBeAg expression and viral replication kinetics that reflect the true viral replication.[3] In contrast, human hepatocyte damage is minimal and peripheral blood alanine transaminase (ALT) levels are normal throughout this phase. Clonal hepatocyte proliferation and DNA integration at the nucleus level are supportive findings.[4,5]

Researchers claimed that liver-related deaths and hepatocellular carcinomas (HCCs) may develop in patients with HBeAg positive chronic hepatitis B infection.[6] Contrary to this claim, the cumulative incidence of HCC was only 1.7% among 946 Korean patients at 10 years of follow-up in the largest cohort study.[7] In a historical cohort study, researchers found the 10-year estimated cumulative incidences of HCC rate to be 12.7% in untreated immune-tolerant phase patients, which is not compatible and higher than the results of other studies.[6,8]

Combination treatment with entecavir and pegylated interferon alpha in children in the immune-tolerant phase of HBV infection results in only 3% (2/60) primary endpoint achievement.[9]

Therefore, there is no generally accepted medical treatment option in patients with HBeAg positive chronic hepatitis B infection, and current oral antivirals are not recommended.[10] Clinical trials about HBeAg positive CHB infection have many weakneses. Selection bias prone retrospective and observational design, neglected confounding variables, and low incidence of clinical events within limited follow-up times. To our knowledge, there is no clinical cohort study about HBeAg positive chronic hepatitis B infection from Turkey to date.

In this study, we aimed to present the demographic, laboratory, and clinical characteristics of patients with HBeAg positive chronic hepatitis B infection in tertiary care centers in Istanbul and discuss the relevant updated literature.

Materials and Methods

Patients ≥18 years old with HBeAg positive chronic hepatitis B infection, who were followed up in three tertiary care centers in Istanbul between January 2000 and August 2018, were evaluated by reviewing their electronic and recorded files. The Ethical Committee of Istanbul Medipol University approved this study (Protocol no.: 10840098-604.01.01-E.44136). During the polyclinic interview, consent was obtained from all patients for analysis and publication.

Chronic hepatitis B is defined by at least 6 months of persistent HBsAg. The definition criteria for patients with HBeAg positive chronic hepatitis B infection included serum HBeAg positivity, high serum HBV–DNA level (>1 000 000 IU/mL), and ALT level remaining within the normal range (<40 IU/L) for at least 1 year. Patients with coin-

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Table 1. Baseline characteristics of HBeAg positive chronic hepatitis B infection

Variables	Results
Age, Mean (SD±range)	36 (11.7, 18-78) years
Underlying diseases (n)	CHD (1), CRD (1), HT (5)
Male gender	50 (32%)
ALT (mean±SD)	30±9 IU/ml
AST Platelet Ratio Index (APRI) IQR	1st Qu.: 0.2102; 3rd Qu.: 0.3234
Without antiviral treatment, n	40 (63%)
Follow-up duration, mean (range)	67 (18-180) months
Liver biopsy, n	30 (48%)
First-degree relatives' conditions (n, /)	
Mothers	CHB: (16/62), cirrhosis: (1/62), HCC: (0/62)
Fathers	CHB:(4/62), cirrhosis: (3/62), HCC: (0/62)
Siblings	CHB: (27/138), cirrhosis: (0/138), HCC: (0/138)

SD: Standard deviation; CHD: Chronic heart disease; HT: Hypertension; CHB: Chronic hepatitis B; CRD: Chronic renal disease; ALT: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; IQR: Interquartile range; HCC: Hepatocellular carcinoma.

fections (hepatitis D virus, hepatitis C virus, and human immunodeficiency virus) and those with continuous alcohol consumption were excluded from the study. HBeAg seroconversion was defined as the loss of HBeAg and anti-HBe formation, which were examined twice at a 3-month interval. Serum ALT elevation was defined as exceeding the upper limit of the normal ALT value, which was measured three times in a 6-month period. ISHAK score was used to evaluate the liver histological activity index and fibrosis. AST Platelet Ratio Index (APRI) score was calculated according to the maximum AST and minimum PLT values during the follow-up period.

Whether HBsAg positivity was detected in any of the patients' mothers, fathers, and siblings, or they had been diagnosed with cirrhosis or liver cancer, and whether they had been followed up with these diagnoses in a health facility were recorded by asking the patient.

Results

The mean age of the 64 patients was 30 (SD 11.7, range 18-39) years, and 50% (32) of them were males. During follow-up, 40 patients were followed without treatment, tenofovir disoproxil fumarate was administered in 17 patients, entecavir in 3, lamivudine in 2, and pegylated-interferon alpha-2a in 2 patients. Five patients were treated with more than one drug during the clinical course. Only two patients had been treated with pegylated interferon alpha-2a and lamivudine combination treatment.

The mean follow-up period of the patients was 67 (18-180) months and only 2 of these patients developed spontaneous HBeAg seroconversion without ALT flare. HBeAg (+) chronic hepatitis B developed in 4 of the patients after the immune-active period. No drug treatment was applied in two patients who had HBeAg seroconversion. During follow-up, 30 patients underwent liver biopsy. The mean histological activity index with ISHAK (HAI) was 3/18 (range 2-9/18). ISHAK fibrosis was 0/6 in 18, 2/6 in 3, and 1/6 in 9 patients.

Mothers, fathers, and siblings of 51 patients were questioned about the presence of hepatitis B infection. While 16 of the patients had CHB, only one mother had cirrhosis. The siblings of 27 patients had CHB and none had cirrhosis. Only 4 of the fathers had CHB and 3 fathers were diagnosed with cirrhosis. None of the patients' relatives had HCC in the mean follow-up period of 5.5 (1.5-15) patient years. Table 1 summarized the baseline characteristics of HBeAg positive chronic hepatitis B infection.

Discussion

Discussions on the definition of HBeAg positive chronic hepatitis B infection are continued. Some researchers suggest that the terminology "high viremia, low inflammation" would be more appropriate to define this period.[3] Liver tissue tolerance to acquired immunity-mediated damage prevents tissue damage but leads to viral persistence. Some receptor families show both proinflammatory and anti-inflammatory activities, which determine the fate of the host cell against all stress factors that are mediated by infection or external factors.[11] It is claimed that the accumulation of inhibitor cytokine/chemokine receptors expressed on CD8+ T lymphocytes, particularly in the prolonged process, is associated with inhibition or at least prolongation of the inflammatory process.[11] The same process was thought to have a protective effect on HCC development. Blockage of these specific receptors in HBV animal models is related to the development of HCC.[12] A complex immune process rather than a tolerance state exists in the host-virus interaction.[13]

HBeAg, an important structural protein of the unmutated and replicative HBV virus, has the capacity of blinding the immune response, which may be the cause of long-term tolerance.[14] HBeAg seroconversion is considered to be an important parameter for disease control in the course of the disease or in the follow-up period under oral antivirals. During this phase, the spontaneous HBeAg clearance rate is also very low (<5% per year).[15] Only two of our patients developed HBeAg seroconversion during the follow-up period, and it was noteworthy that these two patients did not receive any antiviral regimen. In addition, ALT elevation, another important indirect indicator of viral clearance, increased in these two patients before the development of HBeAg seroconversion, with a peak value of 136 IU/mL in one patient and 636 IU/mL in the other. Whether the patients were symptomatic during this period or not could not be obtained from the files. This may be considered to be compatible with cytolytic immune clearance.[13]

Researchers claimed that these unfavor risks may occur in a relatively long period of time, and therefore intervention is needed in this patient group.[8] In our cases, there were no unfavor outcomes in terms of cirrhosis and liver cancer development during the follow-up period. HCC was not reported in any of the first-degree family members. More long-term follow-up results are needed to conclude more reliable inferences. Table 2 summarizes the clinical studies of patients with HBeAg positive chronic hepatitis B infection in the medical literature. The lack of a control group and the presence of selection bias in observational and interventional studies are prominent factors as well as biological insignificance for the treatment regimes such as vaccination.

The main limitation of our study is the definition of "the true HBeAg positive chronic hepatitis B infection" phase that is also conceptually controversial. The critiques about a few patients' fibrosis stage upper than stage 1 can be explained by concomitant diseases (alcoholism, fatty liver, etc.). The other critique is treatment indications in some of our HBeAg positive chronic hepatitis B infections that may be related to the change of international guidelines treatment recommendations within follow-up years. Due to the lack of patients' homogeneity, phase definition accuracy, and long-term follow-up time, we need more studies that enroll adult patients with HBeAg positive chronic hepatitis B infection to evaluate their risk of unfavorable outcomes and treatment effectiveness as well.

Table 2. Clinical studies of patients with HBeAg positive chronic hepatitis B infection

Reference	Study type	Patients/ method	Limitation	Statistical method	Outcome analysis	Conclusion
Lee et al. (2020)	RC	946 patients IT CHB patients	Observational	MVA	The cumulative incidence rate of HCC at 10 years was 1.7%	Extremely low risk of HCC development
Lee et al. (2019)	RC	Group 1: IT CHB group (n=126) Group 2: VR group (n=641)	Uncomparable groups Selection bias Relatively small sample size and small event number	PSM and IPTW	10-year cumulative risks of HCC (2.7% vs 2.9%, p=0.704) and (LRE) (4.6% vs 6.1%, p=0.903)	Untreated IT group consistently had a similar prognosis compared with VR group
Wu et al. (2019)	RCT	Immune-tolerant (IT) patients Interventional Group 1: (TDF) and telbivudine (LdT) group (n=60) Group 2: (TDF) group (n=61)	Short term follow-up	DA, CS	HBeAg seroconversion occurred in 5/60 (8.3%) patients in the combination therapy group and 2/61 (3.3%) patients in the (TDF) group at week 48 (p=0.233)	HBeAg seroconversion rate is unsatisfactory in the short term
Rosenthal et al. (2019)	PC	60 children Interventional Entecavir plus pegylated interferon	Lack of control group	DA, CS	2 children (3%) achieved the primary endpoint and were also HBsAg negative and anti-HBs positive	The combination of entecavir and pegylated interferon for up to 48 weeks rarely led to a loss of HBeAg with sustained suppression of HBV DNA levels in children in the immune-tolerant phase of HBV infection, and treatment was associated with frequent adverse events (AEs)
Kim et al. (2018)	RC	413 untreated ITP vs 1497 (IA) Observational	Selection bias Possibility that some patients with advanced fibrosis were included Being a single-center study, the results of the current study may not be generalizable	MVLR IPTW	IT group showed a significantly higher risk of HCC (HR 2.54; 95% CI 1.54–4.18) and death/transplantation (HR 3.38; 95% CI 1.85–6.16) than the (IAP) group	Untreated IT phase patients with CHB had higher risks of HCC and death/transplantation than treated immune-active phase (IAP)
Wong et al. (2018)	LFS	Immune-tolerant (IT) patients received (TDF) and/or emtricitabine for 4 years and were followed for another 4 years after treatment cessation	Lack of control group The sample size was small Unknown fibrosis score Upper limit of normal for ALT was higher than that recommended by the AASL	DA, CS	Not generalizable results	Rapid virological relapse is universal, and clinical relapse is common after stopping antiviral therapy

Table 2 (cont). Clinical studies of patients with HBeAg positive chronic hepatitis B infection

Reference	Study type	Patients/ method	Limitation	Statistical method	Outcome analysis	Conclusion
Chan et al. (2015)	RCT	(TDF) + placebo group vs (TDF) + emtricitabine group		MVLR	In MVA, female sex (odds ratio=7.05; p=0.002) and TDF + emtricitabine treatment (odds ratio=3.9; p=0.01) were associated with a favorable response	TDF and emtricitabine provided better viral suppression than (TDF) alone although rates of HBeAg seroconversion and HBsAg loss were low
Dikici et al. (2003)	RCT	Fifty-one IT patients (children) Interventional (HBV vaccination) Vaccinated vs. unvaccinated	Biological insignificance	DA, CS		IT children with CHB infection showed no difference in the clearance of HBV DNA and seroconversion of HBeAg to anti-HBe

MVLR: Multivariable regression models; IPTW: Propensity score-matching, inverse probability treatment weighting; DA: Descriptive analysis; CS: Compare statistics; TDF: Tenofovir disoproxil fumarate; AASL: American Association for the Study of the Liver; CHB: Chronic hepatitis B; IAP: Immune-active phase; IT: Immune-tolerant; anti-HBs: Anti-hepatitis B surface antigen–antibody; VR: Virological response.

Intervention with current oral antiviral drugs during this period does not seem to be rationale unless well-designed, long-term studies revealed the contrary results. In our small cohort study, HCC development was not observed in patients with HBeAg positive chronic hepatitis B infection and their relatives.

Ethics Committee Approval: The Istanbul Medipol University Clinical Research Ethics Committee granted approval for this study (date: 08.10.2018, number: 10840098-604.01.01-E.44136).

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

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