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

Ferhat Arslan, Ayse Batirel, Naciye Betul Baysal, Haluk Vahaboglu, Ali Mert

Introduction

Hepatitis B virus (HBV) does not have a cytopathic effect. Immune system of the host is the main factor in the progression of the disease. 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 HBV infection. HBeAg positive chronic hepatitis B infection is characterized by high HBeAg expression and viral replication kinetics that reflect the true viral replication. 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.

Researchers claimed that liver-related deaths and hepatocellular carcinomas (HCCs) may develop in patients with HBeAg positive chronic hepatitis B infection. 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. 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.

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.

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. Clinical trials about HBeAg positive CHB infection have many weaknesses. 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 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 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.
HCC and HBcAg (+) chronic hepatitis B infection

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. A complex immune process rather than a tolerance state exists in the host-virus interaction. HBcAg, 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. HBcAg 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 HBcAg clearance rate is also very low (<5% per year). Only two of our patients developed HBcAg 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 HBcAg 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.

Researchers claimed that these unfavorable risks may occur in a relatively long period of time, and therefore intervention is needed in this patient group. In our cases, there were no unfavorable 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 HBcAg 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 regime 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 HBcAg 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 HBcAg positive chronic hepatitis B infection to evaluate their risk of unfavorable outcomes and treatment effectiveness as well.
| 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                             | 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                                                      | 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                                                                      | 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)                                                    | Selection bias                                  | 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                           | DA, CS            | Not generalizable results                                                        | Rapid virological relapse is universal, and clinical relapse is common after stopping antiviral therapy |
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.

**References**

1. Thimme R, Wieland S, Steiger C, Ghrayeb J, Reimann KA, Purcell RH, et al. CD8(+) T cells mediate viral clearance and disease pathogenesis during acute hepatitis B virus infection. J Virol 2007;77(1):68-76.
2. Nathanson N. Viral Pathogenesis and Immunity. Amsterdam, Netherlands: Elsevier; 2007:279.
3. Kennedy PTF, Litwin S, Dolman GE, Bertoletti A, Mason WS. Immune tolerant chronic hepatitis B: The unrecognized risks. Viruses 2017;9(5):96.
4. Mason WS, Gill US, Litwin S, Zhou Y, Peri S, Pop O, et al. HBV DNA Integration and Clonal Hepatocyte Expansion in Chronic Hepatitis B Patients Considered Immune Tolerant. Gastroenterology 2016;151(5):986-998.e4.
5. Tu T, Mason WS, Clouston AD, Shacklef NA, McCaughan GW, Yeh MM, et al. Clonal expansion of hepatocytes with a selective advantage occurs during all stages of chronic hepatitis B virus infection. J Viral Hepat 2015;22(9):737-753.
6. Kim G-A, Lim Y-S, Han S, Choi J, Shim JH, Kim KM, et al. High risk of hepatocellular carcinoma and death in patients with immune-tolerant-phase chronic hepatitis B. Gut 2018;67(5):945-952.
7. Lee HA, Lee HW, Kim IH, Park SY, Sinn DH, Yu JH, et al. Extremely low risk of hepatocellular carcinoma development in patients with chronic hepatitis B in immune-tolerant phase. Aliment Pharmacol Ther 2020;52(1):196-204.
8. Lee HW, Kim SU, Ba attractkhuu O, Park JY, Kim DY, Ahn SH, et al. Comparison between chronic hepatitis B patients with untreated immune-tolerant phase vs those with virologic response by antivirals. Sci Rep 2019;9(1):2508.
9. Rosenthal P, Ling SC, Belle SH, Murray KF, Rodriguez-Baez N, Schwarzenberg SJ, et al. Combination of entecavir/peginterferon alfa-2a in children with hepatitis B e antigen-positive immune tolerant chronic hepatitis B virus infection. Hepatology 2019;69(6):2326-2337.
10. 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.
11. Franz KM, Kagan JC. Innate immune receptors as competitive determinants of cell fate. Mol Cell 2017;66(6):750-760.
12. Zong L, Peng H, Sun C, Li F, Zheng M, Chen Y, et al. Breakdown of adaptive immunotolerance induces hepatocellular carcinoma in HBsAg-tg mice. Nat Commun 2019;10(1):221.
13. Phillips S, Chokshi S, Riva A, Evans A, Williams R, Naoumov NV. CD8(+) T cell control of hepatitis B virus replication: direct comparison between cytolytic and noncytolytic functions. J Immunol 2010;184(1):287-295.
14. Sede M, Lopez-Ledesma M, Frider B, Pozzati M, Campos RH, Flichman D, et al. Hepatitis B virus depicts a high degree of conservation during the immune-tolerant phase in familiarly transmitted chronic hepatitis B infection: deep-sequencing and phylogenetic analysis. J Viral Hepat 2014;21(9):650-661.
15. Tseng TC, Kao JH. Treating immune-tolerant hepatitis B. J Viral Hepat 2015;22(2):77-84.