Outcomes of Patients With Chronic Hepatitis B Who Do Not Meet Criteria for Antiviral Treatment at Presentation

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BACKGROUND & AIMS: **The availability of potent, well-tolerated, oral antivirals with low rates of resistance has led many experts to recommend liberalizing indications for the treatment of chronic hepatitis B (CHB). This study sought to determine the rate of transitions to an active phase of infection, the frequency of treatment initiation, and the clinical outcomes of patients with CHB who did not meet treatment criteria at presentation.**

METHODS: **We reviewed medical records of patients with CHB, seen in the liver clinics at the University of Michigan Health System from 1999 through 2010, who did not receive antiviral treatment within 6 months of presentation. We collected data on transitions between different phases of CHB, hepatitis B e antigen (HBeAg) seroconversion, loss of hepatitis B surface antigen (HBsAg), and the development of hepatocellular carcinoma (HCC). Data analyses were censored or truncated at the time of treatment initiation or development of an outcome.**

RESULTS: **Of the 234 patients analyzed, 52.1% were men (median age, 35 y), 72.2% were Asian, and 81.2% were HBeAg-negative. During a median follow-up period of 51 months, 19.2% of patients transitioned to a more active disease phase and 18.8% started antiviral therapy. Of the 44 HBeAg-positive patients, 4 patients (9%) had spontaneous HBeAg seroconversion. Nine HBeAg-negative patients but none of the HBeAg-positive patients lost HBsAg. The cumulative probability of HBsAg loss among HBeAg-negative patients was 1% at year 5 and 21% by year 10. No patients had flares of icteric hepatitis or hepatic decompensation. None of the HBeAg-positive patients developed HCC, whereas 2 HBeAg-negative patients developed HCC.**

CONCLUSIONS: **Careful monitoring of patients with CHB who did not meet treatment criteria at presentation permits timely initiation of treatment, with a low risk of adverse clinical outcomes, based on a retrospective study with a median follow-up period of 4.3 years. These findings indicate that current guidelines for initiating treatment are appropriate.**

Keywords: Antiviral Agent; Cancer; HBV Infection; Management.

The availability of potent antiviral drugs with a very low rate of antiviral drug resistance makes it possible for almost all patients receiving antiviral therapy for chronic hepatitis B (CHB) to achieve virologic remission.[1,2] Antiviral therapy clearly is indicated in hepatitis B patients with life-threatening liver disease or cirrhosis. For noncirrhotic patients, guidelines from the American Association for the Study of Liver Disease (AASLD), the European Association for the Study of the Liver (EASL), and the Asian Pacific Association for the Study of the Liver (APASL) recommend treatment in patients with high levels of serum hepatitis B virus (HBV) DNA and alanine aminotransferase (ALT) or histologic evidence of moderate-severe inflammation or fibrosis, and lower thresholds for older patients and patients with a family history of hepatocellular carcinoma (HCC).[3–5] All guidelines agree that treatment is not required in the immune tolerance (IT) or inactive carrier (IC) phase; however, guidelines differ in HBV and ALT cut-off values for initiating treatment.

Recent studies have shown that a high serum HBV DNA level is an independent predictor of HCC,[6] and moderate-severe inflammation or fibrosis can be present

Abbreviations used in this paper: AASLD, American Association for the Study of Liver Disease; ALT, alanine aminotransferase; APASL, Asian Pacific Association for the Study of the Liver; CHB, chronic hepatitis B; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IC, inactive carrier; IT, immune tolerance; PCR, polymerase chain reaction; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; ULN, upper limit of normal.

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in patients with a normal ALT level.[7] Data from these studies has led many experts to recommend liberalizing indications for CHB treatment.[8,9] A retrospective study of 369 CHB patients followed up for 84 months found that 30%, 30%, 19%, and 30% of patients who died from non-HCC related liver causes, and 33%, 53%, 23%, and 47% of patients who died from HCC would not meet the treatment initiation criteria of the 2008 United States algorithm, the 2008 APASL, the 2009 EASL, and the 2009 AASLD guidelines, respectively.[8] The investigators concluded that the treatment criteria of these guidelines were too strict; however, 35% of patients in that study had cirrhosis and the treatment criteria for cirrhotic patients should have been applied to those patients. Furthermore, treatment indications were determined solely based on assessment at presentation and did not consider guideline recommendations for monitoring patients who did not meet the treatment criteria such that treatment can be initiated later when liver disease becomes active.

We studied a cohort of CHB patients who were not receiving antiviral treatment to determine the rate of transitions to an active phase of infection and the frequency of treatment initiation during long-term follow-up evaluation, and the clinical outcomes of patients who remained untreated.

Methods

Study Design

Medical records of hepatitis B surface antigen (HBsAg)-positive patients seen in the liver clinics at the University of Michigan Health System between January 1999 and January 2010 were reviewed retrospectively. Of the 570 CHB patients identified by International Classification of Diseases, 9th revision, codes (070.22, 070.30, 070.32, and 070.33), 245 patients who did not receive antiviral treatment at presentation or within 6 months of presentation met the study criteria (Supplementary Figure 1). All patients had HBV DNA and ALT monitoring every 3 to 6 months during the first year and every 6 to 12 months thereafter. All patients included in this study had at least 2 HBV DNA and 3 ALT measurements during the first year and a median of 4 (range, 1–20) HBV DNA and 5 ALT (range, 1–27) measurements after the first year. The protocol was approved by the institutional review board.

Patient demographics and family history of HCC at baseline visit, HBV markers (hepatitis B e antigen [HBeAg] and antibody, HBV DNA); hepatic panel, platelet count, prothrombin time/international normalized ratio, liver imaging, and liver histology at baseline and at each follow-up visit were recorded. A value of 40 U/L was used to define the upper limit of normal (ULN) for ALT. A secondary analysis was performed with an ULN of ALT of 19 for women and 30 for men.

Serum HBV DNA level was quantified by polymerase chain reaction (PCR) assays: the Amplicor HBV monitor test (Roche Molecular Diagnostics, Indianapolis, IN) with a lower limit of detection of approximately 40 IU/mL between 2000 and 2005, and real-time PCR assay COBAS TaqMan HBV (Roche Molecular Diagnostics) with a lower limit of detection of 29 to 300 IU/mL between 2005 and 2012, and Abbott RealTime HBV Assay (Abbott Molecular, Inc, Des Plaines, IL) with a lower limit of detection of 10 IU/mL from May 2012 onward.

Definitions of Phases of Chronic Hepatitis B Virus Infection

Phases of chronic HBV infection at presentation were determined by HBeAg status, and serum ALT and HBV DNA levels during the period from 6 months before to 6 months after the first clinic visit. Definitions of phases of chronic HBV infection are shown in Table 1.

Definitions of Transitions Between Phases

Transitions between phases were determined by HBeAg status, serum ALT levels, and HBV DNA levels at follow-up visits. Timing of transitions was defined as the date when that transition first occurred; if the patient fluctuated between different phases, then the date when transition to the last phase first occurred was considered.

Outcome Measures

Definitions for outcome measures were as follows: HBeAg seroconversion was defined as loss of HBeAg and detection of hepatitis B e antibody in an HBeAg-positive patient; HBsAg loss was defined as undetectable serum HBsAg in a patient who was HBsAg positive; hepatitis flare was defined as an increase in ALT level to more than 5 times the ULN; severe hepatitis flare was defined as a hepatitis flare with an international normalized ratio

Table 1. Definitions of Phases of Chronic HBV Infection

	HBV DNA level, *IU/mL*	ALT level, ×ULN[a]
HBeAg-positive patients		
IT phase	≥20,000	<ULN
Mildly active phase	≥20,000	1–2× ULN
Immune active phase	≥20,000	>2× ULN
Low replication phase	<20,000	Any level of ALT
HBeAg-negative patients		
IC phase	<2000	<ULN
Indeterminate phase	<2000	>ULN
	>2000	<ULN
Mildly active phase	2000–20,000	>ULN
	≥20,000	1–2× ULN
Immune active phase	≥20,000	>2× ULN

[a]ULN for ALT is according to the traditional cut-off value of 40 U/L.