

Chronic Hepatitis B Infection

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Despite universal vaccination, chronic hepatitis B (CHB) continues to be a major health burden worldwide. Over 400,000 people worldwide are chronically infected with hepatitis B virus (HBV), are at increased risk of developing hepatocellular carcinoma (HCC) and cirrhosis. HBV infected persons need regular lifelong follow-up [1,2]. HBV infection is common with major clinical consequences worldwide. In Asian Americans, the HBsAg carrier rate ranges from 7 to 16%; HBV is the most important cause of chronic hepatitis, cirrhosis, and HCC [3].

Turkey Liver Research Association's throughout Turkey in 2010, according to a survey conducted in Turkey is estimated to be 3 million people with chronic hepatitis B. Hepatitis B virus carriers, representing 4% of HBsAg, hepatitis B virus immune status of anti-HBs 32%, anti-HDV positivity was found to be 2.7%. HBsAg positivity rates by region of HBV is most commonly seen in regions of Central and Southeastern Anatolia Region, at least seen the eastern regions of the Aegean and Central Anatolian region [4,5].

Of the estimated 50 million new cases of HBV infection diagnosed annually, 5-10% of adults and up to 90% of infants will become chronically infected, 75% of these in Asia where hepatitis B is the leading cause of chronic hepatitis, cirrhosis and HCC. Prevention of HBV infection thorough vaccination is still, therefore, the best strategy for decreasing the incidence of hepatitis B-associated cirrhosis and HCC [6].

The diagnosis of CHB is made using a combination of serological, virologic, biochemical, and histologic markers. The natural history of HBV infection can be divided into four phases: immune tolerance, immune clearance (HBeAg-positive chronic hepatitis B), inactive HBsAg carrier, and reactivation (HBeAg-negative chronic hepatitis B). Patients in the immune clearance and reactivation phases, with elevated alanine aminotransferase (ALT) and HBV DNA levels, are candidates for antiviral therapy [7].

The presence of HBV replication markers--hepatitis B e antigen (HBeAg) or HBV DNA--is associated with continuing hepatitis activity or intermittent hepatitis flares and subsequent disease progression, including hepatic decompensation and development of liver cirrhosis or HCC. The average rate of spontaneous HBeAg seroconversion is 10% per year. About 2.1% of patients with chronic type B hepatitis develop cirrhosis each year. The ultimate outcome of chronic HBV infection appears to depend on the duration and severity of liver injury during the immune clearance phase. About 2.1% of patients with chronic type B hepatitis develop cirrhosis each year. The development of HCC related to the severity of the underlying liver disease. The annual incidence of HCC is only 0.1% in asymptomatic HBsAg individual, 1% in patients with chronic hepatitis B, but increases to 3-10% in patients with cirrhosis. The outcome of HBV-infected persons with 'spontaneous' seroclearance of HBsAg is usually favourable, though progress to cirrhosis and HCC is still possible [8,9].

Natural history and outcome, severity of liver damage and need for liver biopsy and antiviral treatment differ significantly between these groups of patients. It is not always easy to distinguish between inactive HBV carriers and patients suffering from HBeAg-negative chronic hepatitis with transient disease remission, as they share similar biochemical (normal serum ALT values) and virological (HBeAg negativity and low HBV DNA levels) features. In clinical practice, it is very important to differentiate inactive carriers from patients with

chronic hepatitis B with spontaneous transient remission [10]. Liver biopsies usually were scored by using the modified histology activity index score of Knodell and the Ishak fibrosis score [11].

The primary determinant of treatment outcomes for CHB is suppression of serum HBV DNA, and long-term suppression of viral replication is likely to reduce progression to cirrhosis and HCC [7]. Candidates for antiviral therapy include patients with moderate-to-severe liver disease as determined by elevated alanine aminotransferase and/or liver biopsy and elevated HBV DNA levels above 2000 IU/mL, per evidenced-based guidelines [3].

The approval of potent oral antiviral agents has revolutionised hepatitis B treatment since 1998. Current antiviral treatment options for CHB include interferon alfa-2b, peginterferon alfa-2a, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. In patients with HBeAg-positive CHB, antiviral treatment is indicated when the serum HBV DNA level is 20 000 IU/mL and the ALT level is elevated. For HBeAg-negative patients, the threshold for initiation of therapy is lower, i.e., a serum HBV DNA level 2 000 IU/mL in association with an elevated ALT level. The presence of at least moderate necroinflammation and the presence of fibrosis on liver biopsy may be useful in supporting the decision to initiate therapy, particularly in patients with normal ALT levels. While undergoing therapy, patients require monitoring every 3 to 6 months to ensure adherence to therapy [7,12]. Pegylated interferon, tenofovir and entecavir are the first line drugs of choice for needing treatment (1). Patients with cirrhosis and detectable HBV DNA must receive antiviral therapy [3]. Tenofovir and entecavir are effective and safe for long-term use in patients with compensated or decompensated cirrhosis from HBV infection [13].

Considerations for treatment include pregnant women with high viremia, coinfecting patients, and those requiring immunosuppressive therapy [3]. Co-infection with HBV does not have a negative impact on the efficacy of anti-HCV treatment, but HBV-DNA should be monitored to overcome the risk of HBV exacerbation [14].

All patients undergoing cancer chemotherapy or immunosuppressive therapy should be screened for hepatitis B surface antigen (HBsAg) and given HBV antiviral prophylaxis if positive [1]. Reactivation of chronic hepatitis B virus infection often occurs in HBsAg positive patients undergoing immunosuppressive or chemotherapy, but can also occur in HBsAg negative, anti-HB core positive patients. The use of lamivudine results in rapid suppression of serum HBV DNA, improves the outcome and enables the continuation of immunosuppressive and chemotherapy [15]. The clinical presentation of reactivation is variable ranging from an asymptomatic course to severe hepatitis, liver failure, and death. It

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is most frequently observed in patients with lymphoma treated with rituximab and corticosteroids as well as in patients undergoing stem cell and bone marrow transplantation. Other risk groups include patients with solid tumors, subjects infected with human immunodeficiency virus, organ transplant recipients, and those with autoimmune diseases (i.e., inflammatory bowel disease, rheumatoid arthritis) [16].

Adults with CHB have an increased risk of death, hepatic decompensation and HCC [4]. In HBsAg-positive patients with risk factors, lifelong surveillance for HCC with alpha-fetoprotein testing and abdominal ultrasound examination at 6-month intervals is required [3].

The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-HBV (REVEAL-HBV) study from Taiwan illustrated the strong association between HBV-DNA level at study entry and risk of HCC over time. In this community-based cohort study, male gender, older age, high serum alanine aminotransferase level, positive hepatitis B e antigen, higher HBV-DNA level, HBV genotype C infection, and core promoter mutation are independently associated with a higher risk of HCC [17]. Those with the next highest level of evidence include aflatoxin exposure, and heavy alcohol and tobacco use for HCC [18].

Family history of HCC multiplies the risk of HCC at each stage of HBV infection. Patients with a family history of HCC require more intensive management of HBV infection and surveillance for liver cancer [19,20].

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