REVIEWS

A Treatment Algorithm for the Management of Chronic Hepatitis B Virus Infection in the United States: An Update

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Chronic hepatitis B (CHB) is an important public health problem worldwide and in the United States, with approximately 25% of patients infected as neonates dying prematurely from cirrhosis or liver cancer. A treatment algorithm for CHB previously developed and published by a panel of United States hepatologists was revised based on new developments in the understanding of CHB, the availability of more sensitive molecular diagnostic testing, the addition of new treatments, and better understanding of the advantages and disadvantages of approved therapies. This updated algorithm is based on available evidence using a systematic review of the scientific literature. Where data are lacking, the panel relied on clinical experience and consensus expert opinion. Serum HBV DNA can be detected at levels as low as 10 IU/mL using molecular assays and should be determined to establish a baseline level before treatment, monitor response to antiviral therapy, and survey for the development of drug resistance. The primary aim of antiviral therapy is durable suppression of serum HBV DNA to the lowest levels possible. The threshold level of HBV DNA for determination of candidacy for therapy is 20,000 IU/mL or more for patients with hepatitis B e antigen–positive CHB. A lower serum HBV DNA threshold of 2000 IU/mL or more is recommended for patients with hepatitis B e antigen–negative CHB, and 200 IU/mL or more for those with decompensated cirrhosis. Interferon alfa-2b, lamivudine, adefovir, entecavir, and peginterferon alfa-2a all are approved as initial therapy for CHB and have certain advantages and disadvantages. Issues for consideration include efficacy, safety, incidence of resistance, method of administration, and cost.

This hepatitis B virus (HBV) treatment algorithm was developed by a panel of US hepatologists and originally was published in 2004.[1] Since then 2 additional therapies, entecavir (Baraclude; Bristol-Myers Squibb, Princeton, NJ) and peginterferon alfa-2a (Pegasys; Roche, Nutley, NJ), have been approved by the US Food and Drug Administration for the treatment of chronic hepatitis B (CHB). In light of the availability of these new agents and new knowledge regarding the natural history of CHB, the panel met again to reassess and revise its recommendations. The aim was to build on the previously published practical and comprehensive algorithm for the diagnosis, treatment, and monitoring of patients with chronic HBV infection in the United States. New data were identified for review by the panel based on independent research by panel members that was aided by a structured literature review and assessment of current treatment guidelines.[2–4] The structured literature review included a comprehensive search of the PubMed computerized bibliographic database for English-language articles published between January 1, 2003 and July 28, 2005 that evaluated the treatment of CHB. In addition, hand searches of bibliographies from relevant articles and consultations with experts in the field yielded additional references. By using explicit inclusion and exclusion criteria developed to evaluate the acceptability of a publication, a total of 37 of 455 reports identified were accepted and abstracted. An additional 28 abstracts from the following conferences also were

Abbreviations used in this paper: AFP, α-fetoprotein; ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; PCR, polymerase chain reaction; US, ultrasound; YMDD, tyrosine-methionine-aspartate-aspartate.

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accepted for inclusion in the evidence table: Digestive Disease Week 2004 and 2005, American Association for the Study of Liver Diseases Annual Meeting 2003 and 2004, and the European Association for the Study of the Liver Annual Meeting 2004 and 2005. Selected abstracts from the American Association for the Study of Liver Diseases Annual Meeting 2005 were added later.

Before the meeting, panel members evaluated the appropriateness of various treatment options in structured clinical scenarios corresponding to key decision points in the algorithm. A 9-point rating scale was used to highlight agreement or divergence of opinion with respect to appropriateness. This information was used to explore the reasons for any divergence and to help the group to reach consensus. Where possible, the panel's recommendations are based solidly on evidence, but where data are lacking panel members relied on their own clinical experience and expert opinion. The algorithm aims to assist the treating physician in answering the practical questions of what tests to order and how to interpret the results, which patients to treat, when and how long to treat, what the available treatment options are, and how to monitor patients. The cost of treatment has not been considered in reaching these recommendations because of the lack of cost-effectiveness data for all of the drugs licensed for treatment of CHB.

Burden of Disease

It is estimated that worldwide at least 350 million people are chronically infected with HBV.[5] Although the prevalence of HBV infection in the United States is lower than in many other countries, an estimated 1.25 million individuals are infected with the virus.[6] However, the prevalence of CHB in the United States is likely to be underestimated. The prevalence of HBV infection among foreign-born persons immigrating to the United States from Asia, the middle East, and Africa ranges from 5% to 15% and reflects the pattern of infection in the country of origin. The size of the Asian American population has increased significantly over the past decade, and currently is estimated to be approximately 10.5 million people.[7] A recent cross-sectional survey of Chinese, Korean, and Vietnamese individuals conducted in several large US cities reported a hepatitis B surface antigen (HBsAg) seroprevalence rate of 10.4%,[8] and a retrospective survey of the Asian American population in the city of New York found a remarkable 23% with detectable serum HBsAg.[9] Despite a 67% decrease in the incidence of acute hepatitis B during 1990 to 2002, attributed in part to broader use of the hepatitis B vaccine,[10] new infections with HBV remain common. It is estimated by the Centers for Disease Control and Prevention that approximately 70,000 people in the United States become acutely infected each year.[11] Individuals with CHB are at increased risk for developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC), and it is estimated that approximately 25% of patients infected as neonates die prematurely from cirrhosis or liver cancer.[5] It is estimated that up to 5000 people die each year in the United States from these complications of HBV infection.[12]

Natural History and Terminology

After acute HBV infection, approximately 3%–5% of adults and up to 95% of children fail to produce an immune response adequate to clear the infection;[5,13,14] in these persons, chronic HBV infection develops. The clinical terms used for the stages of chronic HBV infection and the criteria used in their diagnosis, adopted at the National Institutes of Health Workshop on Management of Hepatitis B,[2,15] are summarized in Table 1. Other clinical terms relating to HBV infection are summarized in Table 2.

The onset of chronic HBV infection is marked by the continued presence of HBsAg, high levels of serum HBV DNA, and the presence of hepatitis B e antigen (HBeAg) in serum. In adult-acquired disease, the early phase of infection often is accompanied by marked disease activity, with increased alanine aminotransferase (ALT) levels, whereas in perinatally acquired disease, patients tend to have normal ALT levels (immune tolerant phase). The activity of disease can accelerate in the latter group, with increased ALT levels, but this usually does not occur until adulthood. HBeAg seroconversion (defined as loss of HBeAg and gain of antibody to HBeAg [anti-HBe], occurring either spontaneously or treatment-related) is most common in the phases when ALT levels are increased. Loss of HBeAg and seroconversion to anti-HBe usually are preceded by a marked decrease in serum HBV DNA levels to less than 20,000 IU/mL,[16] and typically are followed by normalization of ALT levels. Thus, HBeAg seroconversion usually represents a transition from CHB to an inactive HBsAg carrier state in which there is little evidence of hepatitis clinically and lower levels of serum HBV DNA. Some patients also lose HBsAg, which is referred to as *resolution* of HBV infection. However, in the majority of patients CHB is controllable but not usually curable.

A proportion of patients who undergo HBeAg seroconversion have a return of high levels of HBV DNA and persistent or intermittent increases of ALT levels. These patients have a naturally occurring mutant form of HBV that abolishes or down-regulates HBeAg production,

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