

## **Advances in Management of Viral Hepatitis**

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Hepatitis B virus (HBV) is more complex and less understood than hepatitis C virus (HCV), and its management is becoming increasingly complicated with the growing array of therapies available, said Dr. Harvey Alter.

The hepatitis B virus was discovered in 1965 by geneticist Baruch Blumberg, who detected the HBV antigen in the serum of Australian Aborigines. Dr. Alter began working as a researcher with Dr. Blumberg; both shared an interest in studying people with HBV antibodies and screening them for the HBV antigen. Their investigation initially focused on inherited polymorphisms, but expanded to people who had received multiple transfusions when HBV was found to be similarly prevalent (10%) among leukemia patients. Individuals with hemophilia were also found to have high HBV prevalence and carrier rates. It gradually became evident that HBV was not an inherited trait but an infectious disease.

HBV is a globally distributed virus, but is more concentrated in certain areas of world, particularly sub-Saharan Africa, China, and Southeast Asia. Currently, 350 to 400 million people worldwide have chronic HBV, 40% of whom may develop cirrhosis, liver failure, and hepatocellular carcinoma, Dr. Alter reported.

To understand the management of HBV, it is necessary to understand its molecular organization, and how the HBV virus and antigens appear and disappear. HBV is a genomic virus enveloped by hepatitis B surface antigen (HBsAg) and with HBV DNA at its core. Treatment is directed against nucleosides, to suppress hepatitis B viral replication.

The course of HBV infection is highly dependent on the age and mode of acquisition, and the viral genotype. Vertical transmission is particularly important, with a 90% transmission rate and a 90% chance that the infant will be a chronic carrier. The introduction of HBV vaccination at birth in 1980 has reduced the risk of acquiring HBV by 94%. Global eradication programs could eradicate HBV in the same way as has been done with smallpox, Dr. Alter said.

In Europe and the United States, most infections occur in adults by blood transfusion, by needlestick via intravenous drug use, and by sexual transmission. The main genotypes transmitted in the developed world are A, D, F, and G, with genotype A more responsive to interferon treatment than the others. Genotype D, most prevalent in the Mediterranean, predisposes for mutations in the core region of HBV that can lead to severe hepatitis B e antigen (HBeAg) negative status, Dr. Alter said. In Asia, the main genotypes are B and C, which do not respond to interferon and are associated with more severe liver disease and a higher prevalence of hepatocellular carcinoma.

Chronic HBV infection has six stages, which inform decisions about treatment and management:

- Immune tolerance
- Chronic HBeAg positive status
- Chronic HBeAg negative status

- HBeAg mutants
- Inactive HBsAg carrier
- Resolution

The general principles of treatment are that a high proportion of people – those who are immune tolerant or are carriers in an inactive state – do not need treatment. Nonetheless, their alanine aminotransferase (ALT), HBV DNA, and HBeAg levels must be monitored for any change in status. For patients with elevated levels and chronic HBV, the primary goal is to lower levels as much as possible. Seroconversion can be achieved with a number of drugs available for first-line therapy, but patients should still be carefully monitored during low replication for changes in status and progression to fibrosis, cirrhosis, end-stage liver disease, hepatocellular carcinoma, viral reactivation, and the development of mutations.

Several drugs are available for the treatment of HBV: interferon alfa-2b, lamivudine, adefovir dipivoxil, entecavir, peginterferon alfa-2a, and telbivudine. Lamivudine, adefovir dipivoxil, entecavir, and peginterferon alfa-2a are generally used for first-line treatment, to drive down HBV DNA to undetectable levels and possibly achieve conversion to anti-HBeAg. Genotype, HBV DNA, and ALT levels help determine the best candidates for treatment.

In addition, US Food and Drug Administration licenses are in the pipeline for three nucleotide and nucleoside inhibitors that have advantages over current treatments, including high effectiveness, low toxicity, oral administration, and low cost. However, the challenges of these new therapies include less durable response and frequent resistance, Dr. Alter said.

The approved algorithm for the treatment of HBeAg+ patients with low levels of HBV DNA (<20,000 IU/mL) is to not treat. Patients with high levels of HBV DNA ( $\geq 20,000$  IU/mL) should be monitored every 3 to 12 months if the ALT level is normal. Biopsy should be considered in patients older than 35 years, with administration of treatment if significant disease is found. First-line treatment options for patients with elevated ALT levels are adefovir dipivoxil, entecavir, and peginterferon alfa-2a, and possibly telbivudine.

Guidelines for HBeAg- patients tend to recommend treatment sooner – the trigger level for treatment is 2,000 IU/mL rather than 20,000 IU/mL. Treatment is not suggested for patients with low levels of HBV DNA (<2,000 IU/mL), but they should be monitored every 6 to 12 months, Dr. Alter said. The recommendation for patients with high HBV DNA levels ( $\geq 2,000$  IU/mL) is treatment with the same drugs as for HBeAg+. HBeAg- patients with elevated ALT levels require long-term treatment. The goal of HBeAg- treatment is to bring high HBV DNA levels down to undetectable levels. However, once treatment is stopped, only a small proportion of patients are able to maintain the treatment effects.

A number of new oral agents for the treatment of both HBeAg+ and HBeAg- are in clinical trials. The emergence of resistance to antiviral therapies is a key problem, Dr. Alter said. With longer-term therapy, patients may develop drug-resistant strains and inadequate biological response to treatment. These patients are switched to another therapy.

Dr. Alter noted that the cumulative incidence of resistance for lamivudine is 71%, compared with the much lower resistance of newer drugs such as entecavir (16%) and adefovir dipivoxil

(29%). Lamivudine is rarely used as a first-line option given the frequent development of resistance and the superior treatment options available.

When therapy is stopped, 80% of patients with HBeAg+ can sustain seroconversion and negative HBV DNA levels for 6 to 12 months. However, HBeAg- patients will require long-term suppression of HBV DNA to very low or negative levels. Several years of undetectable HBV DNA levels in these patients may decrease the relapse rate, Dr. Alter concluded.