

HBV JOURNAL REVIEW

Volume 5, Issue 7

July 01, 2008

Hepatitis B

Christine Kukka

Experts Explore When a Patient Should Be Treated, and What the First Hepatitis B Treatment Drug Should Be

Leading experts on hepatitis B virus (HBV) infection addressed a variety of important treatment issues at a recent Clinical Care Options workshop.

When Should You Treat Hepatitis B?

Anna S. F. Lok, MD, director of clinical hepatology at the University of Michigan at Ann Arbor, discussed when to treat hepatitis B. She explained that physicians should answer three key questions before beginning treatment:

- How active or ad-

vanced is the HBV-related liver disease now?

- What is the risk that a patient will progress to cirrhosis or severe liver damage or cancer in the next 10-20 years?
- And, what is the chance that once viral load (HBV DNA) is lowered from a limited course of treatment, it can be maintained for up to 3-5 years?

Example 1: Lok the case of a 27-year-old woman who had a high viral load but normal alanine aminotransferase (ALT) levels, which indicates no liver damage was occurring. This is called the immune tolerant stage, which is common in younger patients. Doctors are uncertain whether to treat this group of patients.

While liver damage is

still possible when a patient has high viral loads and normal ALTs, it occurs most frequently in patients age 40 and older, she noted. Given the risks of viral resistance from long-term antiviral treatment and the lack of success of interferon in patients with normal ALT levels, she did not recommend treatment in immune-tolerant patients who were younger than 35 years of age.

Example 2: Lok explored whether to treat a 30-year-old woman with high viral load and normal ALTs, and who also had a family history of liver cancer in HBV-infected relatives. It is unclear whether the family “clusters” of HBV-related liver cancer is related to genetic or environmental factors or a more virulent strain of HBV, Lok

HBV Journal Review

A publication of the Hepatitis C Support Project

Executive Director

Editor-in-Chief,
HCSP Publications
Alan Franciscus

Contributor

Christine Kukka

Managing Editor,

Webmaster
C.D. Mazoff, PhD

Contact Information:

The Hepatitis C Support Project

PO Box 427037
San Francisco, CA 94142

www.hbvadvocate.org

© 2008

Hepatitis C Support Project

noted. While some experts advocate treating all patients with a strong family history of liver cancer, even if they are in the immune tolerant stage, “it must be emphasized that there are no data to support the hypothesis that antiviral therapy can completely prevent liver cancer and there is no model to predict the risk of cancer in this patient. The potential benefits of antiviral therapy must be balanced against the risks of years of antiviral therapy that may indeed be lifelong, and those potential risks must be weighed particularly carefully for a young woman who might be planning to start a family in the near future,” she explained.

Lok stressed that treatment is recommended if there is a high risk of liver damage and death in the next 5 to 10 years, and if there is a good chance of achieving or maintaining low HBV DNA throughout treatment.

Treatment is not recommended if the risk of liver damage over the next 20 years is low, or if there is the possibility of achieving low viral load after a

defined course of treatment is low, she added.

Should you use interferon or an antiviral first?

Ira M. Jacobson, MD, medical director of the Center for the Study of Hepatitis C at Weill Medical College of Cornell University, tackled what treatment to use first in patients who qualified for treatment.

Pegylated interferon, which boosts the immune system, requires a weekly injection for up to one year, and may cause side effects such as depression and fatigue--while oral antivirals cause few side effects. But starting a patient on antivirals, “for most clinicians ... is tantamount to the decision to continue (antiviral) therapy indefinitely,” Jacobson explained. As a result, interferon is favored for first-line therapy in patients who test negative for the hepatitis B “e” antigen (HBeAg-negative), but it is also a recommended option for HBeAg-positive patients.

In HBeAg-positive patients, interferon causes HBeAg seroconversion (loss of “e” antigen and development of the “e” anti-

body) in 30% of patients after one year of treatment, compared to a 12% to 23% seroconversion rate after one year of antiviral treatment. However, researchers are discovering that longer-term antiviral treatment also causes seroconversion, with a 30% seroconversion rate after two years of treatment, and a 40% rate after three years.

Interferon, however, has the advantage of inducing permanent clearance of the hepatitis B surface antigen (HBsAg), which indicates a patient has nearly cleared the infection. Interferon causes 3% to 8% of HBeAg-positive patients to lose HBsAg.

Antivirals such as adefovir (Hepsera), lamivudine (Epivir-HBV) and telbivudine (Tyzeka) cause a HBsAg loss of less than 1% after one year of treatment and entecavir causes a 2% loss of HBsAg after one year. However, HBeAg-positive patients lost HBsAg at a rate of 5% and 3% after two years of treatment with entecavir (Baraclude) or lamivudine, respectively. In a recent trial of tenofovir (Viread-an anti-

ral that is expected to be approved soon by the U.S. Food and Drug Administration), 3% of HBeAg-positive patients lost HBsAg after one year.

In HBeAg-negative patients, one year of interferon produces a sustained undetectable HBV DNA level, which continues in about 20% of patients four years after treatment ended.

Which antiviral to use first?

Doctors should select an antiviral that will cause the least viral resistance, experts say. All experts agree that the antiviral lamivudine should never be used as a patient’s first antiviral treatment unless it’s used to prevent reactivation in inactive HBsAg carriers who receive chemotherapy, which weakens the immune system. HBV quickly develop “resistance” to lamivudine at a rate of 23% after one year, and up to 71% after four or five years of treatment.

The two antivirals recommended as first-line choices are entecavir and adefovir.

Tenofovir has been commonly used “off-label” by doctors and has been used for years

in HIV-infected patients, confers a much higher level of viral suppression than adefovir and should replace adefovir as the preferred antiviral for first-line therapy along with entecavir once the FDA approves it, according to Jacobson.

When should you use an antiviral combination?

There are no clear guidelines, but some clinicians routinely use two antivirals to prevent any potential viral cross-resistance in the following patients:

- Those who already have developed resistance to one drug or more drugs, such as lamivudine and adefovir
- Those who have cirrhosis, in whom it is critical to avoid a hepatitis “flare” or sudden resurgence of viral load and liver damage.
- And, those with HIV-HBV coinfection, in whom it is important to prevent the development of antiviral resistance by either virus.

When can you stop using an antiviral?

Patients who seroconvert while on antivirals face a 10% to

25% risk of reverting back to HBeAg-positive status. But despite that risk, doctors recommend that patients make an attempt to discontinue treatment, although treatment should be continued for at least 6-12 months after seroconversion to reduce the risk of seroreversion.

For HBeAg-negative patients, there is a paradox – it is easier for them to achieve undetectable viral load on antivirals, yet more than 95% will relapse if therapy is discontinued after one year. As a result, antiviral use should be continued indefinitely because of the risk of relapse is so great.

Researchers Consider Using Antivirals During Third Trimester of Pregnancy to Prevent HBV Transmission

While antivirals are used in pregnant HIV-infected women to lower viral load and prevent transmission to newborns, this preventive antiviral treatment is rare in pregnant, HBV-infected women. However,

even with immediate administration of the hepatitis B vaccine and HBIG (hepatitis B antibodies) in newborns, between 5-10% of newborns still contract HBV infection from their mothers, due to the mother’s high viral load. Researchers also believe some HBV strains or genotypes are also more effective at infecting newborns.

In China, there has been some experimentation with administering lamivudine in pregnant HBV-infected women during the third trimester of pregnancy to prevent HBV transmission. During the Clinical Care Options conference, Dr. Jacobson suggested that tenofovir and telbivudine may also be used in pregnant women with HBV. They are both category B drugs, considered safe during pregnancy, and tenofovir has reportedly been used to prevent HIV transmission in pregnant women. However, to date the FDA has not approved any antiviral for use during pregnancy to prevent HBV transmission.

Longer Treatment with Conventional Interferon Improved Success Rate

While most doctors use pegylated interferon today to treat hepatitis B, Chinese researchers tried using conventional interferon, the first interferon developed to treat hepatitis B, for just six months in a control group of 127 HBeAg-positive patients and for an average 10 months or longer in 247 HBeAg-positive patients to see if the extended treatment would benefit patients.

The interferon treatment in the second, study group continued for as long as viral load was decreasing and ranged from 6 to 24 months. According to researchers’ report in the June 2008 issue of the *Journal of Viral Hepatitis*, when treatment ended 39% in the study had achieved normal ALT levels and low viral load, compared to 24% in the six-month treatment control group. After a three-year follow-up period, 40.5% of the study group maintained healthy ALT levels and low viral load, compared to 33% in the

control group. Interferon-alpha treatment tailored in length demonstrated significantly increased effectiveness, researchers noted.

Severe Fibrosis More Common if Patients are Male, Older, and Have High ALT Levels

Chinese researchers evaluated when Asian patients with HBV began developing liver fibrosis (inflammation) and cirrhosis (scarring) by performing “transient elastography,” a procedure involving sound waves that can assess the condition of liver tissue.

According to their report in the June 2008 issue of the *American Journal of Gastroenterology*, severe fibrosis was documented more frequently in older patients, reaching 20% in patients 65 years and older. Higher prevalence of severe fibrosis was seen in HBeAg-positive patients who were age 45 or older, compared to HBeAg-negative patients (58% vs. 43% respectively), and in patients with higher viral loads and ALT levels. Patients who had received anti-

viral treatment had lower ALT levels and prevalence of cirrhosis.

Researchers concluded that the prevalence of severe fibrosis was 34% in the study group, with higher rates of fibrosis associated with older patients, males, and those with elevated ALT levels.

Occult Hepatitis B Can Transmit Infection Through Blood Donations

Historically, HBV is not considered a threat when blood donors have hepatitis B surface antibodies present, but several months after a blood transfusion, two patients developed acute hepatitis B, according to an article by Slovenian researchers published in the June 2008 *Journal of Hepatology*.

A sample from the donated blood contained core and surface antibodies, but it also contained HBV DNA. Increasingly, researchers are recognizing that “occult” hepatitis – with no HBsAg or even surface antibodies – can still contain HBV DNA and transmit infection.

Tenofovir and Lamivudine Combination Effective in Patients with Cirrhosis Who Don’t Respond to Adefovir

Six patients with cirrhosis who did not respond to, or developed viral resistance to adefovir were treated with a combination of tenofovir and lamivudine for six months minimum. South Korean researchers monitored their response to see how effective the combination therapy was against adefovir-resistant hepatitis B.

Reporting in the journal *Liver International*, the researcher wrote that HBV DNA became undetectable in four patients after six months, and in all six patients after 12 months of treatment. ALT levels became normal in four patients after 12 months of treatment.

“This study suggests that this combination may be a promising rescue therapy for these patients, particularly those with liver cirrhosis or pre-existing lamivudine resistance,” the researchers noted.

Silymarin Cures Liver Inflammation Quickly in Laboratory Rats

Researchers are beginning to analyze and test the benefits of silymarin, a traditional liver herbal treatment found in milk thistle, in improving liver health when viral infection occurs. Taiwanese researchers studied the impact high doses of silymarin had on the liver of rats, whose livers had inflammation and fibrosis.

They reported in a recent issue of the *Journal of Viral Hepatitis* that liver fibrosis significantly decreased in rates treated with silymarin.

HBV Genotype Has Little Impact on Antiviral Success, But Plays a Prominent Role in Interferon’s Success

German researchers reviewed 20 studies that linked treatment success, such as HBeAg seroconversion and decline in viral load, to patients’ HBV genotype to explore whether hepatitis B treatment should ever be guided by a patient’s

genotype.

Writing in the journal *Antiviral Therapy*, they concluded that response to antiviral treatment was not “significantly influenced by HBV genotype in HBeAg-positive or HBeAg-negative individuals.”

“In contrast,” they noted, “HBV genotypes are informative concerning responses to interferon treatment in all patients with genotype A versus D and in HBeAg-positive patients with genotype B versus C. “Interferon may be considered as first-line therapy in all genotype A patients and in individuals with genotype B who are HBeAg-positive,” they concluded.

Past HBV Infection Worsens Hepatitis C Prognosis, Weakens Interferon’s Effectiveness

Two studies found that infection with HBV, common in many patients infected with the hepatitis C virus (HCV), worsens patients’ disease progression and limits the success of interferon treatment.

In a recent article in *Liver International*, Brazilian researchers evaluated 31 HCV carriers who had previously been exposed to HBV, but were not currently infected. Compared to HCV patients without a past HBV infection, these patients had more liver damage and inflammation.

They concluded that after 20 years of HCV infection, advanced liver fibrosis could be expected in 13% of those who acquired HCV before the age of 30 but had no prior HBV infection, and in 57% of those infected with HCV after age 30 who had a prior HBV infection.

In another study, Turkish researchers, writing in the May 2008 *Netherlands Journal of Medicine*, examined the impact of interferon on patients currently coinfecting with HBV and HCV. Researchers evaluated their response to conventional or pegylated interferon combined with the antiviral ribavirin (the recommended treatment for hepatitis C) on patients, whose average age was 47.

Fourteen patients were given standard interferon either alone

or in combination with ribavirin, and 12 were given pegylated interferon and ribavirin. None tested positive for HBV DNA but all had HCV RNA and elevated ALT levels. Only two patients (one from each group) cleared the HCV following treatment.

Researchers concluded that neither pegylated nor conventional interferon were highly effective for HBV-HCV coinfection, in which the dominant virus was HCV.

