

HBV JOURNAL REVIEW

Volume 4, Issue 6

June 01, 2007

Hepatitis B

Christine Kukka

Conference Report: When to Treat, What to Use and Whom to Treat for Hepatitis B

Researchers and physicians who specialize in hepatitis B treatment assembled in Washington D.C. in May for the annual Digestive Disease Week conference. Dr. Nancy Reau, assistant professor of gastroenterology and a gastroenterologist at the Center for Liver Disease at the University of Chicago, summarized the latest information about treatment.

When to Treat?

Researchers continue to wrestle with when treatment is necessary. Historically, physicians treated patients when alanine aminotransferase (ALT) levels, which are

released when liver cells are damaged or die, are twice the normal level because that appeared to indicate serious liver damage. Doctors also looked for the presence of the hepatitis B “e” antigen (HBeAg) and whether HBV DNA levels, which show the amount of viruses in the bloodstream, were high and exceeded 100,000 copies/mL.

Doctors have assumed people with normal ALT levels and low viral loads were not experiencing liver damage from infection with the hepatitis B virus (HBV).

During the conference, researchers admitted that ALT levels do not accurately reflect liver health. In a study of patients who had liver biopsies before participating in a drug trial, doctors were surprised to find that two-thirds of patients with only moderately

elevated ALT levels had significant liver damage and scarring.

Researchers still agree that continually elevated ALT levels combined with high viral load indicate a high risk of liver cancer development. And, those individuals with persistently low ALT have the lowest risk for liver cancer, though one small study did demonstrate that even patients with long-term low HBV DNA levels had some liver damage.

“All of these studies serve to highlight that no patient with hepatitis B remains immune to complications, and no parameter can be used to identify a subset of patients that does not need close clinical follow-up,” Reau stressed.

Other methods, including new approaches to monitor cell death, are needed to truly evaluate

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

© 2007

Hepatitis C Support Project

the health of hepatitis B patients and indicate when treatment is needed, she added.

What's the Best Treatment?

With two interferons and four antiviral medications approved by the U.S. Food and Drug Administration (FDA) for adults, it remains unclear how and when to use these medications.

During the conference, two-year data from the telbivudine (Tyzeka) GLOBE trial, showed the antiviral was far more effective than lamivudine (Epivir-HBV) – the first antiviral approved for HBV treatment, which researchers now know causes antiviral resistance rapidly. Antivirals generally work to disable the reproductive abilities of normal viruses, but HBV with mutations are able to continue to keep replicating despite lamivudine treatment. These HBV become the “majority” virus and often can “resist” other antivirals too.

Sixty-three percent of HBeAg-positive patients treated with telbivudine (Baraclude) (vs. 48% treated with lamivudine) achieved lower viral load, normal ALT

levels and development of the HBeAg antibody (called seroconversion). Fifty-six percent of telbivudine patients achieved undetectable HBV DNA, compared to 39% on lamivudine.

Among the HBeAg-negative patients, 78% of telbivudine patients (vs. 66% on lamivudine) achieved a response, and 82% of telbivudine patients (vs. 57% on lamivudine) achieved undetectable viral load at Week 104.

But development of antiviral resistance is a concern for all patients who take antivirals because use of one drug predisposes patients to resistance against other antivirals.

In the GLOBE study, 46 of 115 of the patients who initially responded to telbivudine treatment developed antiviral resistance and 32 quickly experienced a rebound in HBV DNA and ALT levels as the antiviral lost its effectiveness against the telbivudine-resistance HBV.

Ultimately, resistance to telbivudine at Week 92 was 21.8% in HBeAg-positive patients and 8.6% in HBeAg-negative patients.

If doctors can identify viral resistance before

viral load and ALT levels increase and switch the patient to a new antiviral, treatment is much more effective. But doctors fear they will run out of effective antivirals for long-term treatment.

What Role Does Genotype Play?

There are a variety of strains or genotypes of HBV, depending on the region where the virus originated. What role these genotypes play is unclear. While research suggests that genotype may impact how patients respond to treatment and how quickly liver damage occurs, doctors still don't consider genotype when making treatment recommendations. “However, the importance of drug resistance testing is rapidly manifesting,” she wrote, especially when treating a patient who doesn't respond to treatment.

Also, some patients who have never been treated with antivirals already have viral-resistant HBV mutations, and so certain antivirals should be avoided for this group of patients. For example, one study found 14.8% of 108 untreated patients had pre-existing HBV with

lamivudine-resistant mutations.

How Important Is Drug Potency?

Studies presented at the conference confirmed that the antivirals telbivudine and entecavir reduce viral load in HBeAg-positive, previously untreated patients faster than the antiviral adefovir (Hepsera).

Pegylated Interferon Effective in Patient with HBsAg Mutation

Increasingly, researchers are finding patients who have a unique mutation in the surface antigen (HBsAg), or outer covering of the virus. In these patients, the HBsAg has mutated and HBV can continue to replicate even if the antibody to the HBsAg is present.

Normally, the presence of the surface antibodies indicates the virus has been eradicated, but in these patients, viral load continues to be elevated and liver damage can occur.

According to a report published in the June 2007 issue of *Liver Inter-*

national, doctors in Argentina treated a 43-year-old male patient with this HBsAg mutation and genotype A with pegylated interferon.

The patient developed “e” antibodies, cleared the surface antigen and experienced improved liver health after 24 weeks of treatment.

Adefovir Resistance Higher When Only Adefovir Is Used After Lamivudine Resistance Develops

Hong Kong researchers treated 56 patients who had developed viral resistance to lamivudine with either adefovir alone, or with lamivudine plus adefovir, for three months and then followed them for 15 months to see which treatment approach was more effective.

They reported in the 2007 issue of *Antiviral Therapy* that normal ALT levels occurred in 25 (89%) of the adefovir group compared with 24 (86%) in the combination group. Lowered viral load occurred in seven (35%) of the adefovir group at 12 months,

compared with five (28%) in the combination group.

By 24 months, seven (64%) in the adefovir-only group achieved lower HBV DNA compared with two (40%) in the combination group.

Adefovir resistance after 24 months occurred in 18% of the adefovir-only group, compared to 7% in combination group.

While there was little difference between the two treatment approaches, researchers noted that additional studies with longer follow-up times are needed to evaluate whether combination therapy was better at reducing the risk of adefovir resistance.

HBV with Core Promoter Mutations Less Responsive to Interferon

A group of Chinese researchers, working in a laboratory, experimented to see if HBV with core promoter mutations, often associated with HBeAg-negative hepatitis B infection, could resist interferon.

Reporting in the August 2007 issue of *Antiviral Research*, the researchers isolated HBV with these mutations, which allow

them to replicate without secreting the “e” antigen.

These mutated HBV produced the same amounts of HBsAg as non-mutated or wild-type HBV, but the amount of HBeAg secreted was about 35% less than wild type HBV.

After interferon was added, HBeAg, HBV DNA and HBV replication rates decreased for both the wild-type HBV (by 25.7%, 31.8%, 29.8%, respectively) and the mutated HBV (by 8.4%, 27.4%, 10.1%, respectively).

As a result, researchers concluded that these mutated HBV could still replicate despite interferon treatment.

Researchers Find HBV Genotype D Has Mutations That May Evade Vaccination Protection

A team of Italian researchers examined HBV from 99 patients with HBV genotype D to see what mutations or unique genetic make-up exists in this strain of HBV.

Their report, published in the April 2007 issue of *Virology*, reported that this genotype had HBsAg mutations that

were apparently able to survive despite introduction of surface antibodies.

Researchers are concerned that during immunization with just the surface antigen, the body usually creates surface antibodies that target the non-mutated or wild surface antigen. However, in the case of this genotype, the vaccine-induced antibodies did not recognize this mutated surface antigen and were unable to prevent chronic infection with this strain of HBV.

“Our results suggest that careful surveillance of vaccine-induced escape mutants should be considered in populations with highly frequent genotype D infections,” they wrote, and the results raise questions about how prevalent and virulent the genotype D strain may be.

Scientists Find Connection between Hepatitis B and Fatty Liver Disease

A research team from South Korea, reporting in the May issue of *Gastroenterology*, say the HBx protein produced by the HBV is directly linked to excess deposits and accumulation of fat in the

liver, which can cause damage and scarring.

The discovery was made using a genetically modified mice model to test the effects of highly active HBx proteins on the liver.

Fatty liver affects roughly a quarter of the population in developed countries and is associated with diabetes, high blood pressure and lipoprotein disorders.

Viral Mutations, Cirrhosis and High Viral Load Are All Risks for Liver Cancer

Hong Kong researchers examined HBV genotypes, core promoter viral mutations, HBV DNA levels and cirrhosis to search for what factors contributed most to development of liver cancer in 248 HBV-infected patients with liver cancer and 248 infected patients without cancer.

Writing in the May 2007 issue of *Gut*, they reported that patients with HBV genotype C, certain mutations, viral load exceeding 10,000 copies/mL and cirrhosis had a higher risk for cancer compared to patients with genotype B, no viral mutations, low viral load

and no cirrhosis.

Specifically, patients with mutations and cirrhosis had a 21.3-fold increased risk of liver cancer, compared to patients with mutations, but no cirrhosis.

Patients with mutations and high HBV DNA levels had a 7.2-fold increased risk of cancer, compared to patients with mutations and low viral load.

The highest risk was among those patients with high viral load, mutations and cirrhosis.

Clevudine Effective in HBeAg-Positive Patients, 59% Achieve Undetectable HBV DNA

A report on the effectiveness of the experimental antiviral clevudine, administered for 24 weeks in 182 HBeAg-positive patients, found the treatment to be effective when administered at 30 mg daily dose, according to a write-up in the May 2007 issue of *Hepatology*.

Average HBV DNA reductions at week 24 were 100,000 copies/mL. At week 24, 59% of patients in the clevudine group had undetectable

HBV DNA levels and that suppressed viral load continued for 24 weeks after therapy ended.

About 68% of patients achieved normal ALT levels, and maintained those healthy levels during the 24 weeks after treatment ended. No viral resistance to clevudine was detected during the 24-week treatment period.

Immune Tolerant Stage Ends on Average at Age 31, Researchers Conclude

French researchers, writing in the May 2007 issue of the journal of *Clinical Gastroenterology and Hepatology*, report that the immune tolerant phase of HBV infection may last until patients reach about age 31, based on their study of 40 patients.

The immune tolerant phase occurs when people are infected during early childhood. Their immune systems fail to notice the infection, produce antibodies or attack the HBV-infected liver cells. As a result, HBeAg is usually present, viral loads are often high, but ALT levels are normal.

The researchers per-

formed liver biopsies on the immune tolerant patients and found no fibrosis in 20 patients, and mild fibrosis in 20 patients. During a follow-up period of 37.7 months in 31 patients, researchers noted that 12 patients emerged from their “immune tolerant” phase at about age 31 (38%). Six transitioned to an inactive disease state (low viral load and ALT levels), three had chronic hepatitis (elevated viral load), and three had intermittent spikes in ALT, indicating their immune systems were attacking the infected liver cells.

The researchers concluded that liver biopsies were probably not needed in patients in the immune tolerant stage of hepatitis B. “Loss of tolerance, occurring at a median age of 30.7 years, is characterized by a rapid transition to an inactive carrier state in two-thirds of patients, and to chronic hepatitis in one third of patients,” they noted.

Mother-to-Child Infection Risk Much Higher with HBV Genotype C

Japanese researchers examined the genotype of 116 HBV-infected

children to see what role genotype played in the spread of the infection between parents and children.

According to their report published in the April 2007 issue of the *Journal of Medical Virology*, of 91 children who contracted the infection from their mothers, 88 (97%) had HBV genotype C. The number of children with genotype C who were infected by their mothers was significantly higher than those with genotype B, D, or A.

“In conclusion, HBV genotypes influence not only clinical characteristics (disease progression) but also the mechanisms of interpersonal HBV transmission,” they wrote.

Tenofovir Effective in HIV-HBV Coinfected Patients with Cirrhosis

A recent issue of the *Journal of Antiviral Therapy* reviewed the effectiveness of the antiviral tenofovir in patients who have cirrhosis (severe liver scarring) and are coinfecting

with HIV and HBV.

Tenofovir, approved by FDA for treatment of HIV, has also been found to be an effective treatment tool against hepatitis B, but its effectiveness in patients with cirrhosis was not known.

Australian researchers monitored seven cirrhotic coinfecting patients treated with tenofovir. Four patients were HBeAg-positive.

After tenofovir treatment for 28 months, three patients lost HBeAg and two developed “e” antibodies. One patient was removed from the liver transplant waiting list because he improved.

The potential reversal of end-stage liver disease with tenofovir treatment may be a critical treatment tool for this population, researchers concluded.

Hepatitis B Not Directly Tied to Increased Stroke Risk

An increased risk of stroke or heart attack does not result directly from HBV infection, researchers reported in the May issue of *Stroke*, but may be a

byproduct of liver disease.

British and South Korean researchers investigated reports of an increased risk of stroke and myocardial infarction (MI) among hepatitis B patients by following more than 521,000 men aged 30 to 64 years from 1990 to 1991.

Testing positive for HBsAg was associated with a decreased risk of ischemic stroke and MI and an increased risk of hemorrhagic stroke, but the risks for stroke and MI were similar between HBsAg-positive and -negative men if there was no liver dysfunction.

But men with both HBsAg and liver damage had a higher risk of stroke.

The findings, the researchers point out, do not support the theory that HBV infection plays an important role in causing MI or strokes. “Rather,” they concluded, “decreased coagulation status in HBV-associated chronic liver dysfunction appeared to increase the risk of hemorrhagic stroke while reducing the risk of ischemic stroke and MI.”

HBV Increases Risk of Liver Cancer in People with Hepatitis C Infection and Cirrhosis

A report, published in the May 2007 issue of the *Annals of Internal Medicine*, determined that exposure to HBV increases the risk of liver cancer in patients already infected with the hepatitis C virus (HCV) who have cirrhosis.

Although researchers have suggested that people with hepatitis C are more likely to develop liver cancer if they have also been exposed to HBV, they did not know how much this actually increases risk of liver cancer.

They studied 846 HCV-infected patients from 1995 to 2005. About 52% of the group who had cirrhosis had also been exposed to HBV and they were more than one and a half times as likely to develop liver cancer as those without HBV infection.

