

HBV JOURNAL REVIEW

Volume 4, Issue 7

July 01, 2007

Hepatitis B

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40% of Older, Asymptomatic Hepatitis B Carriers Clear the Infection

A surprising number of older adults infected with the hepatitis B virus (HBV) clear the hepatitis B surface antigen (HBsAg) over the course of their lives, according to a report published in the May 2007 issue of the journal *Hepatology*, which followed HBV-infected Taiwanese adults over decades.

Spontaneous HBsAg clearance, without treatment, has been considered a rare event in chronically-infected adults. However, researchers noticed that chronic HBV infection in Taiwan declined from 15% to 20% in those

younger than age 40, to 5% to 10% after age 60 or 70.

This decline prompted researchers to monitor 1,965 adults (55% males, average age 36), who tested positive for the hepatitis B “e” antibody, for more than 10 years. They found that 245 patients cleared HBsAg, on average, at age 48.

They found their adults had an 8.1% chance of HBsAg clearance after 10 years, but the clearance rate increased dramatically in this asymptomatic population to 24.9% and 44.7%, respectively, after 20 and 25 years.

“Cumulative rate of HBsAg seroclearance in asymptomatic adult carriers from high endemic areas was approximately 40% after

25 years of follow-up,” they wrote. “The low HBsAg seroclearance rates in previous studies might be due to the relative short period of follow-up.”

Researchers Study Impact of Early HBeAg Ser-conversion in Children

Taiwanese researchers studied the viral loads (HBV DNA) in 58 chronically-infected children who spontaneously lost the hepatitis “e” antigen (HBeAg) and developed the “e” antibody (anti-HBe).

The children had normal alanine aminotransferase (ALT) levels when they enrolled in the study. Researchers monitored the children’s

HBV Journal Review

A publication of the Hepatitis C Support Project

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viral load, ALT levels, genotype or viral strain and occurrence of precore mutations in their HBV, annually over the 10-year study period.

Following HBeAg seroconversion (development of “e” antibodies), 35 children continued to have low or undetectable HBV DNA. However, 23 continued to have high, fluctuating viral loads.

The average age of the child at enrollment was 7, the average age when ALT levels were highest was 13, the average age of HBeAg seroconversion was 17, and the age at last follow-up was 24.

The precore mutation appeared more often in children who continued to have fluctuating, high viral load than in the group with consistent low viral load after seroconversion (61% versus 23%). HBV genotypes had no effect on viral load after seroconversion, researchers noted. After HBeAg seroconversion, none of the children had persistent, abnormal ALT levels.

Reporting in the June edition of *Gastroenterology*, re-

searchers wrote, “Generally, these young seroconverters had decreased viral loads, normal ALT levels, and uneventful courses after HBeAg seroconversion. A longer follow-up period is necessary to elucidate the significance of HBeAg seroconversion occurring in childhood and young adulthood.”

High Leptin Levels May Signal Liver Damage and Poor Response to Lamivudine

Greek researchers studied 25 people infected with HBeAg-negative hepatitis B and 25 infected with the hepatitis C virus (HCV) to see what relationship existed between the severity of their liver disease and the levels of leptin in their blood. Leptin is a hormone produced by fat cells, which tells the brain how much hunger is present in order to regulate storage of body fat. It plays a key role in the body’s energy levels.

Reporting in a recent edition of the BMC’s

Gastroenterology, the researchers analyzed the effect of body composition and leptin levels with the degree of liver damage and effectiveness of antiviral treatment.

They found that patients with cirrhosis (severe liver scarring) had higher leptin levels than those with only mild fibrosis. They also found that hepatitis B patients with lower leptin levels responded better to antiviral treatment with lamivudine (Epivir-HBV), than those with higher leptin levels.

“Our data clearly suggest that cirrhosis due to (HBV or HCV) is associated with higher leptin levels,” they wrote.

HBV Antiviral Drug Entecavir May Cause HIV Drug Resistance

When treating patients coinfecting with HBV and HIV, physicians should be aware that a recent study, published in the June 21, 2007 issue of the *New England Journal of Medicine*, found that the antiviral ente-

cavir (Baraclude) used against hepatitis B could lead to HIV drug resistance.

Earlier studies indicated that entecavir had no impact on HIV replication, researchers noted, and so doctors have assumed it was safe to use to treat hepatitis B in coinfecting patients.

But doctors reported that three coinfecting patients treated with entecavir for their HBV infection experienced changes in their HIV viral levels and CD4 (infection-fighting) cell counts. The HIV viral load fell 10-fold and CD4 counts rose. While that appears to be good news, HIV can quickly become resistant to antiviral drugs, so physicians must use caution whenever treating HIV with antivirals that can cultivate drug resistance.

Unless a patient is already on a fully suppressive anti-HIV regimen, treating with entecavir runs the risk of generating HIV resistance to reverse transcriptase inhibitors.

In one of the patients, entecavir treatment led to the development of HIV muta-

tions that could “resist” or continue to replicate despite treatment with lamivudine and emtricitabine (Emtriva).

Researchers reported that they were able to discern the anti-HIV effects of entecavir – while earlier studies had not – because they used more sensitive tests.

Tenofovir More Effective Than Adefovir in Phase III Clinical Trial

Tenofovir (Viread), an antiviral developed to treat HIV infection, proved to be more effective against hepatitis B than the antiviral adefovir (Hepsera) in a Phase III clinical trial announced recently.

Gilead Sciences Inc., creator of both tenofovir and adefovir, used a daily 300 mg dose in the trial. At week 48, about 71% of the 250 patients treated with tenofovir had undetectable HBV DNA levels and improvement in their liver health, compared to 49% of 125 patients treated with adefovir.

The most common

side effects reported during the study were minor abdominal pain, back pain and headaches, and were on par with side effects from adefovir.

A second Phase III trial of tenofovir, involving HBeAg-positive patients, is scheduled to be completed later this year.

Tenofovir Is an Effective Long-term Treatment in HBV-HIV Coinfected Patients

Tenofovir offers an effective long-term treatment for hepatitis B as well as HIV according to two studies presented at the Third International Workshop on HIV and Hepatitis Coinfection in Paris. The studies, on primarily men, conducted in London and Duesseldorf, also found that tenofovir was effective in patients who developed viral resistance to lamivudine (Epivir-HBV).

Tenofovir reduced HBV DNA (the amount of HBV in the blood) to undetectable in 83% of patients af-

ter 58 months of treatment in the British study.

In the Duesseldorf study, after four years all 12 patients in the study achieved undetectable HBV DNA levels and 83% had normal ALT levels.

Fathers Also Transmit HBV to Children, Underscoring Need for Vaccination

While researchers know mothers commonly transmit HBV to children, there has been little research to determine the risk HBV-infected fathers pose to children. Writing in the July 2007 issue of the *Journal of Medical Virology*, a group of Japanese researchers tracked father-to-child transmission by closely analyzing the molecular make-up of the HBV in eight infected children and their fathers in five families.

The study revealed that “father-to-child transmission is an important route of HBV infection in Japan,” and researchers recommend that universal vaccination against HBV infection be in-

stituted immediately in Japan for all children when either parent is infected with HBV.

When Adefovir Replaces Lamivudine, Non-Mutated or Wild-Type HBV Reappear

What happens to HBV with mutations that allow them to “resist” the antiviral punch of lamivudine when lamivudine is replaced with the antiviral adefovir? South Korean researchers, writing in the July 2007 issue of the *Journal of Medical Virology*, carefully analyzed HBV to see how they responded when adefovir was used.

They monitored molecular changes in 14 lamivudine-resistant patients whose HBV DNA had rebounded when lamivudine no longer slowed their HBV replication. Their HBV were monitored 3, 6 and 12 months after adefovir treatment began.

Viral load dropped 10,000-fold after 12 months, and HBV with lamivudine-

resistant mutations (called YMDD mutations) that were identified in 12 patients declined and actually disappeared and were replaced by non-mutated or “wild” type HBV in six patients.

Core promoter mutations, found in 12 patients, were replaced by wild-type virus in three patients (25%), while precore mutations found in four patients were replaced by the wild-type in three patients (75%) after adefovir treatment.

Results show that adefovir can reverse the number of HBV with mutations, and suppress the virus effectively, they noted.

Interferon Treatment After Liver Cancer Surgery May Improve Survival

According to an article published in the *Annals of Surgery*, treatment with immune-boosting interferon after surgery to remove liver cancer tumors may improve survival in HBV-

infected patients.

Liver cancer, resulting from years of active HBV infection and liver damage, is difficult to treat. Surgeons attempt to remove liver tumors, but liver cancer commonly returns.

Doctors tried treating a group of HBV-infected patients, who had tumors removed, with interferon. An untreated group served as the control.

At one year, survival rates were 97% in the interferon-treated group and 85% for the control group. At five years, survival rates were 79% in the interferon group and 61% for the control group.

Among patients with more advanced cancers, survival at five years was 68% for the interferon group, compared to 24% in the control group.

The researchers concluded that treatment with interferon following the complete surgical removal of liver cancer significantly improved survival, especially among patients with more advanced disease.

Doctors Recommend Lowering Viral Load Before Starting Chemotherapy for Liver Cancer

In the June issue of *Hepatology*, researchers evaluated the impact of HBV DNA levels on patients with liver cancer who received chemotherapy. They found that patients with high pre-chemotherapy levels of HBV DNA had an increased risk of reactivated infection and worse survival.

For most patients whose liver cancer is inoperable, chemotherapy remains one of the key treatment options, even though the survival rate is low.

Researchers at the Chinese University of Hong Kong followed 125 HBV-infected liver cancer patients before and during chemotherapy. The average survival was 6.8 months. Patients with high pre-treatment HBV DNA had a significantly higher incidence of developing severe hepatitis during chemotherapy and had poorer survival.

“Based on the present findings, the incorporation of antiviral therapies to reduce HBV viral load should be considered as part of management for (liver cancer) patients undergoing chemotherapy,” they wrote.

HBV-Infected People Have Higher Rates of Non-Hodgkin’s Lymphoma

Researchers at the Josephine Ford Cancer Center in Detroit reported in the May 2007 issue of *Hepatology* that adults with chronic hepatitis B were 2.8 times more likely to develop non-Hodgkin’s lymphoma (NHL).

Non-Hodgkin’s lymphoma is cancer that originates in the lymphatic system, the body’s disease-fighting network. Tumors develop from white blood cells (lymphocytes) and can occur at different locations in the body.

Hepatitis C patients have been shown to have higher rates of NHL, and researchers wanted to see if HBV-infected patients also had a higher incidence

of this disease.

They compared the disease rate in 3,888 HBV-infected patients and 205,203 people without hepatitis B.

They reported that people with chronic hepatitis B were 2.8 times more likely to develop NHL than uninfected people.

Hepatitis C Treatment Surprisingly Effective Against Hepatitis B in One Patient

Doctors treating a patient coinfecting with HBV and HCV with the hepatitis C treatment of pegylated interferon and the antiviral ribavirin and were surprised to find that the patient developed surface antibodies, which often signals recovery from hepatitis B.

Pegylated interferon is used to treat hepatitis B also, but the antiviral ribavirin has been used to date only to treat hepatitis C.

The Japanese research team, writing in the June 2007 issue of *Hepatology Research*, reported that

the patient experienced a gain in surface antibodies and a decline in surface antigen (HBsAg) in the early stages of treatment. Simultaneously, the patient's ALT increased, indicating that the immune system was attacking the infected liver cells.

The patient's HBV DNA declined and he lost the HBeAg and gained "e" antibodies.

Ultimately, the patient's surface antibody levels declined, but his viral load continued to be undetectable.

The researchers determined that the interferon and ribavirin somehow stimulated his immune system to attack the HBV infection.

Women, Younger Patients, and Genotypes B or C Respond Best to Interferon

A multinational team of researchers monitored the outcomes of 518 HBeAg-negative patients after 24 weeks of treatment with pegylated interferon with or without lamivudine; or with

just lamivudine.

Writing in the May 2007 issue of *Gut*, they reported that the patients who achieved normal ALTs and low HBV DNA levels after 24 weeks of treatment were those treated with pegylated interferon (either with or without lamivudine). Most of these responders were also younger, female and had elevated ALT levels before starting treatment.

Among those treated with interferon or just lamivudine, patients with genotypes B or C had a higher success rate than those with genotype D. Genotype D patients tended to respond better to the combination of interferon and lamivudine, than with just interferon.

When evaluated one year after treatment ended, about 19% of those treated with interferon with or without lamivudine sustained their normal ALT and low HBV DNA levels, compared to 10% of those treated with just lamivudine.

