

HBV JOURNAL REVIEW

Volume 5, Issue 2

February 01, 2008

Hepatitis B

Christine Kukka

Antiviral-Induced Mutations in the Surface Antigen May Cause Drug- and Vaccine-Resistant HBV

Researchers in Spain studied whether mutations in the protein that surrounds the hepatitis B virus (HBV), called hepatitis B surface antigen or HBsAg, resulted from antiviral treatments in patients coinfecting with HBV and HIV.

They examined HBV from 71 patients (52 coinfecting with HIV-HBV) who were treated with an antiviral for longer than 12 months. All but 13 patients had received lamivudine (Epivir-HBV), and of the rest, 10 HBV-only-infected patients had been treated with adefovir (Hepsera) and three coinfecting patients were treated with tenofovir.

Only lamivudine resistance-associated mutations produced changes in the HBsAg, and lamivudine-resistance was more frequent in HBV genotype A than D.

HBV genotype A was the predominant genotype among HBV/HIV-coinfecting patients.

The triple-HBV mutation that produced changes in the HBsAg antigen-antibody binding was found in three coinfecting individuals.

Researchers, writing in the November 2007 issue of the *Journal of Acquired Immune Deficiency Syndrome*, concluded that antiviral treatment may cause mutations in the HBsAg, particularly among patients with HBV genotype A. "Such mutations might represent a public health concern because of the potential risk of transmission of HBV drug- and

vaccine-resistant strains," they noted. The hepatitis B vaccine's HBsAg antibodies would be ineffective against the HBsAg of these patients.

Mutations in HBsAg Common, and Not Linked to High Viral Load

The gene sequence (the order in which DNA components are arranged in a gene) for HBsAg is used by researchers to identify if HBV from one person infected another. But in a study of 40, untreated patients, whose cumulative history with HBV spanned 210 years, wide variations and mutations were found in all of the patients' HBsAg gene sequences.

The patients the Dutch researchers studied had a mix of viral loads and a hepatitis B "e" antigen status (HBeAg-positive and -negative.) Surpris-

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

ingly, the number of HBsAg mutations was higher in those with low viral loads and lower in those with high viral loads.

Researchers concluded that mutations and variations in HBsAg is widespread, and therefore is of little use when mapping possible chains of HBV infection transmission, according to their report in the *Journal of Viral Hepatitis*.

Hepatitis B Remains a Major Public Health Problem

Infection with HBV continues to be a major public health problem globally and in the United States, according to a report by Kevin Fenton, MD, PhD, FFPH, Director of the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention (CDC), presented at the HEP-DART 2007 Frontiers in Drug Development for Viral Hepatitis symposium.

In the United States, about 45,000 new HBV infections are reported each year, with 90% of the new cases occurring in immigrants. Since the early 1990s, there has been a 25% reduction in acute HVB infection due

to vaccination of high-risk adults and universal immunization of infants. In 2005, 95% of new infections occurred in adults. Individuals at highest risk are men who have sex with men, injection-drug users, and individuals with multiple sexual partners.

In 2006, CDC revised its guidelines and recommended universal vaccination in settings with a high proportion of adults at risk for HBV infection, such as STD clinics, HIV counseling/testing centers, drug treatment centers, and correctional facilities. Barriers to adult vaccination include financial issues, the three-dose requirement, and patient acceptance.

Long-Term Hepatitis B Outlook Good in Caucasians

The majority of Caucasian patients with HBeAg-positive chronic hepatitis become inactive carriers over time, Italian researchers report in the January 2008 issue of *Gut*. Researchers followed 70 HBeAg-positive patients over an average of 25 years and reported that 87% underwent spontaneous HBeAg seroconversion. During the next 22.8 years after seroconversion, 66% became inac-

tive carriers.

Liver-related deaths occurred in 11 patients, five due to liver cancer and six due to liver failure. Overall, 50 patients were alive at the end of follow-up and the cumulative probability of survival was 90% at 10 years and 86% at 25 years. The 25-year probability of survival was 95% in inactive carriers, 50% in patients with HBeAg-negative hepatitis or HBeAg reversion, and 40% in those who were persistently HBeAg positive.

Thymosin Alpha-1 May Be More Effective Than Conventional Interferon in HBeAg-Negative Patients

Chinese researchers compared the effectiveness of thymosin alpha-1 (Zadaxin), an immune booster, against conventional interferon in HBV treatment by analyzing results from four randomized controlled trials including 199 patients. They examined loss of HBeAg (called seroconversion) and drop in viral load (HBV DNA in the bloodstream) in HBeAg-positive patients, and they examined loss of HBV DNA and normalization of alanine transaminases (ALT, which

signals decreased liver damage) in HBeAg-negative individuals.

Researchers reported that at the end of the treatment period, there were not significant differences in patients' responses to either immune-booster drug. But six months after treatment ended, HBeAg-negative patients treated with thymosin alpha-1 responded better than those treated with interferon, according to the report published in the February 2008 issue of *Antiviral Research*.

Experimental Nitazoxanide, Tizoxanide and other Thiazolides Inhibit HBV and HCV Replication

Nitazoxanide (NTZ), effective against bacteria, protozoa, and several viruses in cell culture models, is currently in phase II clinical trials for treatment of hepatitis C virus (HCV) infection. Researchers recently discovered it may also be effective against HBV.

In laboratory settings, NTZ was equally effective at inhibiting replication of non-mutated HBV as well as lamivudine- and adefovir-resistant HBV, according to a report by U.S. researchers in the January

2008 issue of the journal of *Antimicrobial Agents and Chemotherapy*.

Strong T-Cell Response Is Seen During Successful Treatment and HBeAg Seroconversion

The immune system’s T-cells are essential to vanquishing infection, and researchers have assumed that a weak T-cell response to HBV infection is how the infection becomes chronic or long-term.

A multinational research team carefully analyzed T-cell response in patients who were treated with the antiviral adefovir and successfully seroconverted (losing the HBeAg) to see what role the T-cells (CD4+ T-lymphocytes) played.

They analyzed the HBV-specific CD4+ T-cells during 48 weeks of adefovir treatment in 13 patients, and in six patients who received placebo.

Adefovir-treated patients showed increased CD4+ T-cell responses to HBV compared to placebo-treated patients. This enhanced T-cell response peaked at treatment week 16, and was confined to patients who

achieved a great decline of HBV DNA (about a five-fold decline) and HBeAg loss. That strong T-cells response did not occur in the treated patients who experienced only a moderate (three-fold) decline in viral load and remained HBeAg-positive, according to the researchers’ report in the January 2008 issue of the journal of *Antimicrobial Agents and Chemotherapy*.

Tenofovir Effective in Non-Responders to Adefovir, and Tenofovir-Emtricitabine Combo Effective When Adefovir Resistance Is Present

Researchers tried the antiviral tenofovir alone, and in combination with the antiviral emtricitabine, in patients who did not respond to adefovir treatment, or who had developed HBV resistance to adefovir, to see which was most effective. Neither tenofovir, which has been used effectively to treat HIV infection, nor emtricitabine has been approved by the U.S. Food and Drug Administration for treatment of hepatitis B.

Of the 13 nonresponders to adefovir, re-

searchers identified adefovir-resistant HBV in three patients. Of the 13, 10 patients were treated with just tenofovir and eight responded well. One patient with confirmed adefovir resistance who was treated with tenofovir continued to have adefovir-resistant HBV. When emtricitabine was added to the ongoing tenofovir treatment, the patient’s HBV DNA levels declined.

Another patient, who had no adefovir-resistant HBV before treatment, developed adefovir resistance during tenofovir treatment.

All three patients who received the combination treatment achieved undetectable HBV DNA within three to 12 months, including the two who had adefovir resistance before treatment began.

The U.S. researchers, reporting in the January 2008 issue of the *Journal of Hepatology*, concluded that tenofovir alone is effective in patients who do not respond well to adefovir, but the combination of tenofovir and emtricitabine should be considered in patients with documented adefovir-resistant HBV.

Quick Development of Telbivudine Resistance Remains a Concern

U.S. researchers, writing in the December 2007 issue of the journal *Clinical Therapeutics*, examined the effectiveness and viral resistance to the antiviral telbivudine (Tyzeka), which was approved by the U.S. FDA in late 2006.

After 52 weeks of telbivudine treatment (in the Phase III GLOBE study), 3% of HBeAg-positive patients and 2% of HBeAg-negative patients developed viral resistance. After 104 weeks of therapy, 17.8-21.6% of HBeAg-positive and 7.3-8.6% of HBeAg-negative patients experienced a rebound of HBV DNA, which indicates the antiviral is no longer effective due to the high number of resistant HBV.

After 24 weeks of treatment, the risk of resistance was greater in patients with higher viral loads. Telbivudine is not effective against HBV that are already resistant to lamivudine.

Researchers wrote, “Questions concerning the optimal length of therapy and long-term efficacy await the results of on-going clinical trials. Concerns about increas-

ing resistance over time may relegate telbivudine to second-line status in the management of chronic HBV infection.”

A Combination HBV and HPV Vaccine Appears Effective in Early Trials

U.S. researchers are trying to develop a combination HBV and human papillomavirus (HPV) vaccine to use in adolescents who are at high risk of both sexually-transmitted infections. More people are successfully vaccinated when immunizations are delivered in fewer doses.

A study, led by U.S. researchers, assessed the safety and effectiveness of a combination vaccine that would protect against both HBV and genital warts, caused by HPV, which can lead to cervical cancer.

The combination vaccines were administered to 1,877 women, ages 16-23, and produced robust protect antibodies against HPV, but only moderate HBV antibodies. However, 96% of the women eventually achieved adequate HBV antibodies by month seven, according to the report in the January 2008 issue of the journal *Vaccine*.

Rare HBV Genotypes Found in Brazil, Researchers Fear Spread of Lamivudine-Resistant HBV

There are HBV viral strains or genotypes (A-H) with distinct geographical distributions, and each often has different disease progression rates and different responses to antiviral and interferon treatment.

Researchers in Brazil analyzed lamivudine-resistant HBV mutations found in 36 Brazilian patients, half were homosexual men, who had been treated for 12 to 84 months. As expected in Brazil, genotypes A (75%), D (9.3%) and F (3%) were present. However, one sample was from genotype C, rarely found in Brazil, and three samples were from genotype G, which had not been previously detected in Brazil.

Lamivudine-resistant mutations were identified in 62% of HBV DNA-positive samples. Fifteen patients had a lamivudine-resistant double mutation, and two patients had a rare triple-mutation, that includes mutations in the hepatitis B surface antigen (HBsAg), which allows the HBV to reproduce despite vaccination with

surface antigen antibodies.

The three isolates of genotype G were examined and all showed the double mutation plus a large genetic divergence from non-mutated genotype G HBV.

“The identification of genotypes C and G, rarely detected in South America, seems to indicate a genotype distribution different to that observed in non-treated patients,” researchers noted in their report in the January 2008 issue of *BMC Microbiology*. “Disparities in routes of transmission (genotype G seems to be linked to homosexual behavior) and in pathogenic properties (genotype C is very aggressive) among HBV genotypes may explain the presence of rare genotypes.”

Men’s Genes Predispose Them to Higher Risk of Liver Cancer

A fundamental difference in the way males and females respond to chronic liver disease at the genetic level may explain why men are more prone to liver cancer than women, according to , according to an article in *Cancer Research*. Men develop liver cancer at twice the

rate of women in the United States. In other countries, especially in Asia where HBV infection is widespread, the rate for men can be eight or 10 times that for women.

Liver cancer is the fifth most common cancer in the world and the third-biggest killer. Rates in the United States are lower than those in other countries but are rising rapidly, in part due to viral hepatitis infections.

Male and female livers are inherently different, researchers report, with most of the differences arising during puberty when male livers are exposed to periodic bursts of growth hormone. This prompts male livers to develop different genetic material than female livers, which explains why men and women can have different reactions to certain antibiotics and other medications.

The researchers studied mice, which also have higher liver cancer rates among males. The mice were infected with *Helicobacter hepaticus*, which produces the same hepatitis symptoms characteristic of human hepatitis B. When the male mice developed hepatitis, some masculine liver genes were activated and others turned off. At the

same time, some feminine genes were reactivated. This resulted in an unpredictable gene profile termed liver-gender disruption, which prevented the liver in males from maintaining normal functions, which resulted in cancer.

When Is a Liver Biopsy Merited, and Is It Necessary Before Starting Treatment?

William F. Balistreri, MD, medical director of the Liver Transplantation Program at Cincinnati Children's Hospital Medical Center, discussed the role of the liver biopsy in Medscape Gastroenterology's "Ask the Experts About Liver Disease."

A liver biopsy can rule out other causes of liver disease, assess the degree of liver damage, and provide information about disease progression. But the decision to initiate treatment does not depend on the health of the liver, he wrote, and a biopsy generally does not predict how well a patient will respond to interferon or antiviral treatment. The best candidates for treatment can be determined by examining their HBV DNA levels, ALT levels, and antigen and antibody tests.

The best indicators for response to treatment are low HBV DNA levels and elevated ALT levels, he

explained. The decision as to whether to obtain a liver biopsy should take into consideration age, whether the patient has slightly elevated ALT levels, their HBeAg status and HBV DNA levels, and other clinical features that suggest liver damage, he wrote.

The American Association for the Study of Liver Diseases (AASLD) guidelines suggest that patients who are HBeAg positive with HBV DNA levels 20,000 IU/mL or higher after a three- to six-month period of elevated ALT levels, or who remain HBeAg positive with HBV DNA levels 20,000 IU/mL or higher and are over 40 years old, should be considered for liver biopsy, and treatment should be considered if biopsy shows moderate/severe inflammation or significant fibrosis, he noted.

Therefore, liver biopsy is most useful in persons who do not meet clear-cut guidelines for treatment, he suggested. "One could argue that a biopsy could indicate cirrhosis and that the presence of cirrhosis increases the risk for (liver cancer). However, periodic screening for liver cancer should be performed in all patients with chronic HBV infection, even in the absence of cirrhosis," he concluded.

Be Sure to Check Out Our New Hepatitis B Brochure at:

http://www.hbvadvocate.org/hepatitis/factsheets_pdf/ HBV_Bro_07.pdf

