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Hepatitis B

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Entecavir-Resistant Hepatitis B Viruses Often Present in Untreated Patients

Doctors are learning that the hepatitis B virus (HBV) with mutations that allow it to reproduce despite treatment with the antiviral lamivudine (Epivir-HBV) can also “resist” the antiviral entecavir (Baraclude). Researchers set out to learn if entecavir-resistant HBV are present in HBV-infected people who have never been treated with lamivudine.

In an article published in the December 2007 issue of the *Journal of Viral Hepatology*,

researchers reported following 111 patients before and after treat-

ment with lamivudine to see when entecavir-resistant HBV appeared.

Before treatment, three patients (2.7%) had entecavir-resistant HBV, but none had lamivudine-resistant HBV. During treatment, entecavir-associated mutations were detected in 10 (9%) of patients who did not respond to treatment. None of them had entecavir mutations prior to treatment and two of the 10 patients developed entecavir resistance even before lamivudine-resistant HBV appeared.

Researchers concluded that entecavir-resistant HBV are present in a significant number of patients, even before antiviral treatment. “This fact, as well as the emer-

gence of entecavir-resistant variants (mutations) during lamivudine treatment, should be kept in mind when selecting candidates for entecavir therapy,” they wrote.

HIV-HBV Coinfected, Lamivudine-Resistant Patients Quickly Develop Resistance to Entecavir

Japanese researchers, writing in a recent edition of *Hepatology Research*, reported on a patient coinfecting with HBV and HIV who quickly developed HBV resistance to the antiviral entecavir.

The 60-year-old coinfecting man, with HBV genotype H, had earlier been treated with lamivudine. The therapy initially suppressed replication of both

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HBV and HIV, but after two years of treatment, lamivudine-resistant HBV rebounded so he was treated with the entecavir in addition to his HIV drug treatment. His HBV DNA declined slightly for a time, but within six months it rebounded and researchers identified entecavir-resistant HBV.

Researchers recommend that doctors should review other options before treating HIV-HBV coinfecting patients – especially those with lamivudine resistance – with entecavir.

Lamivudine Associated with Several New Viral Mutations, Including the Surface Antigen

Brazilian researchers detailed a number of new and unique viral mutations that occurred in a 58-year-old man infected with HBV who was treated for 33 months with the antiviral lamivudine in a report in the *Journal of Gastroenterology and Hepatology*.

Lamivudine is known to be linked to a “YMDD” mutation in the virus’s genetic material, which allows

HBV to replicate despite treatment with lamivudine. However, this patient experienced a spike in alanine aminotransferase (ALT), an enzyme released by damaged or dying liver cells, 19 months after starting lamivudine treatment. After 32 months of treatment, several other mutations were identified including three hepatitis B surface antigen (HBsAg) mutations.

The patient was hospitalized with severe liver damage, and died one month later, though his viral load remained only at moderate levels during the entire time. Researchers suggest that other lamivudine-associated viral mutations, in addition to the YMDD mutation, can occur.

Mutations in Surface Antigen Vary Widely Over Time, And Appear Unrelated to Viral Load

Dutch researchers analyzed the surface antigen’s gene sequences to see how often the surface protein had mutations. They followed 40, untreated HBeAg-positive and negative patients who had varying viral loads and represented HBV

genotypes or viral strains A through E over a cumulative time span of 210 years.

Their research, reported in the *Journal of Viral Hepatitis*, identified 70 changes (ranging from zero to eight per person) in the surface antigen. Surprisingly, the mutations did not occur more frequently in people with high viral load, and instead happened more frequently in those with moderate viral load.

Years of Universal HBV Immunization Has Resulted in Little Protection for Young Drug Users

After years of mandatory childhood hepatitis B immunization, researchers wanted to see if younger injection drug users (IDU) were less susceptible to hepatitis B due to universal immunization programs and available needle exchange programs.

University of California researchers reviewed the immunization and infection status of 831 IDUs under age 30 in San Francisco and found 21% had current or past infections, 22% had hepatitis B antibodies

associated with vaccination protection, and 56% had no antibodies and were vulnerable to infection.

HBV infection in IDUs was higher among heterosexual males, men who have sex with men, and sexually active women. IDUs with vaccination protection tended to be more commonly female and younger.

Researchers, writing in the *Journal of Viral Hepatitis*, concluded that few young IDUs show evidence of successful immunization and the majority remain susceptible to HBV infection. Targeted and innovative approaches to immunizing young IDUs are needed to prevent future HBV infections, they recommended.

Convenience Key to Effective Vaccination Programs for IDUs

A study, sponsored by the U.S. Centers for Disease Control and Prevention and published in the journal of *Drug and Alcohol Dependence*, examined how to effectively get IDUs, who are at high risk of hepatitis A virus (HAV) and HBV infection, vaccinated. Stud-

ies show this population has low immunization rates, despite their high risk of infection.

Researchers assessed whether convenience and financial incentives would boost vaccination rates among 3,181 IDUs, ages 18-30, in five U.S. cities. They found that 19% and 23%, respectively, had been already exposed to HAV and HBV. While 83% were willing to be vaccinated, only 36% had received one or more vaccine doses. (Two HAV doses and three HBV doses are required.)

By location, the proportion of IDUs who had received one or more doses was as follows: Baltimore 83%; Seattle 33%; Los Angeles 18%; New York 17%; and Chicago 2%. The results showed vaccination was highest when the vaccine was available immediately at a community clinic or center, and participation was lowest when vaccination was offered only after test results had been reported to the individual. When on-site vaccination was unavailable, financial incentives may increase participation, researchers suggested.

Telbivudine Superior to Lamivudine in HBeAg-positive Patients

In a double-blind, phase III trial, 1,370 HBV patients received either 600 mg of telbivudine (Tyzeka) or 100 mg of lamivudine once daily for 52 weeks. At week 52, significantly more HBeAg-positive patients receiving telbivudine had lower HBV DNA (75% vs. 67%) and less liver damage (64% vs. 56%).

In HBeAg-negative and the HBeAg-positive groups, telbivudine appear more effective and caused less viral resistance, according to a report in the December 2007 issue of the *New England Journal of Medicine*.

Tenofovir More Potent Than Adefovir in Lamivudine-Resistant Patient

Dutch researchers followed 10 lamivudine-resistant patients who had the antiviral tenofovir added to their ongoing lamivudine treatment, and then had tenofovir replaced with the antiviral adefovir (Hepsera) to see which

antiviral was most effective.

Tenofovir, effectively used to treat HIV, has proven effective against hepatitis B and is expected to be approved by the U.S. Food and Drug Administration (FDA) for HBV treatment soon.

The researchers, reporting in the *Journal of Viral Hepatitis*, monitored changes in HBV DNA and ALT in the patients. The average treatment period with tenofovir was 78 weeks resulting in a median viral load reduction of 5.4-fold. Two patients experienced a one-fold increase during tenofovir treatment.

After the switch to adefovir, 60% of patients had an increase in HBV DNA, the average increase was 2.8 to 4.5 log¹⁰ copies/mL. Resurgence of HBV DNA occurred most commonly in patients with genotypes B or D and detectable HBV DNA at the time of the switch from tenofovir to adefovir.

Retreatment with tenofovir resulted in a rapid decline in HBV DNA, which demonstrates its potency in comparison to adefovir, researchers noted.

HBV Death Rates Higher in Those Who Drink Excessively

French researchers examined the specific causes of death in 999 citizens who died from liver disease associated with either HBV, hepatitis C, HIV or other liver ailments in 2001.

The number of deaths in the group associated with HBV infection was 1,327 (2.2 deaths per 100,000). Among them, 93% had cirrhosis and 35% had liver cancer. Deaths related to HBV infection occurred at an earlier age in patients with a history of excessive alcohol consumption.

Interferon and Lamivudine Combination Yields Similar Results as Interferon Treatment Alone in Children

Researchers treated 31 children who tested positive for the “e” antigen (HBeAg) with either six months of standard interferon or a combination of six months of interferon with 24 months of lamivudine, to see which treatment regimen improved liver

health the most. Liver biopsies were obtained before and after treatment.

According to their report in the November 2007 issue of the *Journal of Pediatric Gastroenterology & Nutrition*, ALT levels, HBeAg status and HBV DNA levels were not substantially different between the two groups at the end of each treatment regimen.

“Both therapies seemed to be effective in the regression of periportal bridging necrosis,” researchers noted. “In addition, combination therapy was also effective in the regression of intralobular degeneration, focal necrosis, and necroinflammatory activity index.”

A similar study, reported in the December 2007 issue of *Pediatrics International*, examined the benefits of either sequential or simultaneous combination treatment with interferon and lamivudine in 45 children, ages 12 to 14.

Twenty-four children were treated with standard interferon thrice weekly for six months, followed by lamivudine for an additional six months. Twenty-one

children were given interferon and lamivudine simultaneously for six months and then continued lamivudine alone for another six months.

In the sequential group, 13 patients (54.2%) did not respond, five patients (20.8%) achieved normal ALTs and undetectable HBV DNA, and six patients (25%) achieved normal ALTs (except for one patient), undetectable HBV DNA and seroconversion, developing “e” antibodies.

In the simultaneously-treated group of 21 children, 11 (52.4%) did not respond, one case (4.8%) achieved normal ALT and undetectable HBV DNA, and HBeAg seroconversion occurred in seven children (33.3%). This group had a higher sustained response also.

Long-Term Lamivudine Treatment Appears Safe in Children

A team of international researchers examined the safety and long-term effects of lamivudine treatment in 151 children from nine countries who received lamivudine treatment

for up to three years. Researchers monitored their weight, height, HBV markers, ALT levels, and HBV DNA levels.

The children were divided into two groups – those who had achieved virological response (VR), including normal ALTs, undetectable HBV DNA, development of “e” antibody (seroconversion), at three years and those who had not.

Children achieving VR after one year or two years of lamivudine was 82% and 90% respectively, compared to 75% who achieved seroconversion without treatment.

Eight children lost HBsAg during the study – all of them had received lamivudine at some point. Evaluation of safety data revealed no adverse effects related to lamivudine. There was no impact on weight or height. ALT flares were seen in 2% of children, but caused no serious damage.

Favorable outcomes from lamivudine treatment of HBV infection in children are maintained for several years after completion of treatment, researchers

reported.

Non-Invasive Tests for Cirrhosis May Help Avoid Liver Biopsies

New ultrasound and magnetic resonance (MR) imaging tests yield encouraging early results in diagnosing fibrosis and cirrhosis of the liver, according to three studies in the October 2007 issue of the journal *Clinical Gastroenterology and Hepatology*.

Researchers hope these non-invasive imaging techniques may eventually reduce the need for invasive liver biopsies – a procedure that obtains a tissue sample through a needle inserted into the liver to determine the presence and severity of fibrosis and cirrhosis.

Researchers evaluated elastography techniques that evaluate reactions to ultrasound vibrations or energy waves in order to measure the elasticity or stiffness of liver tissue. Lower elasticity or higher stiffness indicates increased fibrosis or cirrhosis.

About 90% of patients with cirrhosis were correctly identi-

fied by ultrasound-based transient elastography. The test was less accurate in detecting less-severe fibrosis.

Because the studies used different cut-off points, the analysis could not establish the true accuracy of this technology. Researchers called for additional studies so the tool could identify all types of fibrosis.

Herbalife Supplement Causes Severe Liver Damage

Researchers have issued another warning about potential damage to the liver from herbal supplements. According to a report by Swiss researchers published in the October 2007 *Journal of Hepatology*, 10 people developed liver damage as a result of taking Herbalife dietary supplements.

Most of the patients were middle-aged and suffered severe liver damage, one case required a liver transplant, after several months of taking the supplement. Researchers encouraged better regulatory oversight and consumer caution of herbal supplements.

Researchers Develop Formula for Liver Cancer Risk

U.S. researchers used patient survival rates to develop a formula or algorithm to identify the risk of liver cancer for people chronically infected with HBV.

Writing in the *Journal of Viral Hepatitis*, researchers reported they categorized risk, based on comparisons with uninfected populations.

Patients who tested positive for chronic HBV for longer than six months were 146 times more likely to develop liver cancer, and people who had tested positive for HBsAg only once were 30 times more likely to develop liver cancer.



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