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Hepatitis B

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Viral Resistance to Adefovir Found in Eight Patients, with Severe Outcomes

A study of eight male patients who had poor response to the antiviral drug adefovir (Hepsera), found the patients developed viral resistance to adefovir within two years and experienced a return of liver damage. While this is a small study, it is the first time that significant resistance to adefovir has been reported.

Some hepatitis B virus (HBV) have genetic mutations that allow them to replicate despite antiviral treatment. Antivirals are designed to disrupt the virus' genetic material to slow or stop viral replication. However, early studies of adefovir found few signs of rapid viral resistance to the drug.

But this report, spearheaded by University of Michigan researchers and published in the September 2005 issue of the *Journal of Hepatology*, found these patients' HBV had mutations that allowed them to replicate despite adefovir treatment. The patients' viral load (HBV DNA) increased, as did their levels of alanine aminotransaminase (ALT), an enzyme released by damaged liver cells.

The men had been treated with adefovir for just one to two years when their viral load and ALT levels began to rise. The failure of the antiviral and rapid rebound of HBV produced severe liver damage in two men, and one died.

“Salvage therapy with lamivudine, entecavir or tenofovir (antivirals) was given to seven patients and a (three-fold) reduction in HBV DNA was seen in three patients,” researchers wrote. “In conclusion, adefovir resistance can be associated with significant viral rebound and hepatic decompensation, which may be fatal.”

Drug Used to Treat Sinus Infections May Put HBV Patients at Risk

Levofloxacin (Levaquin), a pill used to treat adults with sinus, lung and urinary bacterial infections, may cause liver damage or failure in patients with chronic hepatitis B, according to a report in the Au-

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gust 2005 issue of *The Annals of Pharmacotherapy*.

Turkish researchers reported on a 55 year-old woman who was hospitalized with severe liver damage. She had taken levofloxacin (500 mg daily for 10 days) for an upper respiratory infection. She had chronic hepatitis B, which had been asymptomatic for at least 10 years.

The woman died 12 weeks later from liver failure. Doctors identified “levofloxacin-induced fulminant hepatic failure,” as the cause.

“We believe that, in our patient, the relationship between levofloxacin and her illness is clear because of the negative results in the etiological studies, the short time between the drug’s administration and the development of disease, and the pathologic findings suggestive of drug-induced hepatitis,” they wrote. “Clinicians should be aware of the possibility of severe hepatic injury associated with levofloxacin when prescribing this drug.”

Doctors Push for Better Screening of Donor Blood for “Occult” HBV

Current screening for HBV in donated blood may be inadequate, according to a group of Taiwanese researchers writing in the September 2005 issue of the *Journal of Hepatology*, because some donated blood contains HBV DNA, even though it tests negative for the surface antigen (HBsAg).

The researchers found donor blood with “occult” HBV (containing HBV DNA but no HBsAg) infected the recipients, even patients who had been vaccinated against hepatitis B before they received the tainted blood.

Researchers tested 327 patients for six months after they received transfusion. Five (1.5%) developed HBV one week after transfusion. Three of the infected were children who had been vaccinated and had developed surface antibodies from the vaccine. These vaccinated children cleared the infection, but they developed core antibodies, which indicates a past infection.

“Our findings suggested the possibility that occult HBV infection was transmissible by transfusion,” the researchers wrote.

“Moreover, some vaccinated children with anti-HBs (surface antibodies) were still susceptible.”

This blood donor infection rate may be higher in Taiwan than other countries, due to the high rate of HBV infection there.

“Therefore, despite active immunization, sensitive screening assays for occult HBV infection such as nucleic acid amplification test could be considered in endemic areas,” they concluded.

What Is the Difference Between Precore and Core Promoter HBV Mutations?

Writing in *Medscape Gastroenterology’s “Ask the Experts Column,”* doctors addressed the difference between precore and core promoter HBV mutations, which are quite common in chronically infected adults.

HBV have a 10-fold higher mutation rate than other DNA vi-

ruses. Because of this weak genetic “blueprint,” HBV easily mutate to evade the body’s attacking antibodies.

These two common mutations allow the virus to replicate without secreting the “e” (HBeAg) antigen, which in turn allows it to avoid attracting “e” antibodies. A patient with either mutation may have the “e” antibody, but will also have high viral load (HBV DNA) and possible high ALT levels.

Precore mutant HBV have a mutation in the virus’ precore region, which prevents HBeAg production, and is found in regions where genotypes B, C, and D are predominant, such as Asia and the Mediterranean area, where it can be detected in more than half of all people with chronic hepatitis B. It is significantly less prevalent in North America and Europe, where genotype A is more common.

Infection with the precore mutated HBV does not necessarily cause accelerated liver damage, according to the experts.

In contrast, core promoter mutants appar-

ently have the ability to rapidly replicate without HBeAg, causing a higher viral load in the liver, “which triggers liver damage directly or indirectly through the immune response.” The liver damage that ensues from high viral load and the immune system’s effort to attack the infected liver cells can lead to cirrhosis and liver cancer.

As opposed to precore variants, core promoter variants can be detected in patients who are either HBeAg-positive or –negative, the researchers wrote. “The prevalence of the core promoter variant is about 40%; it is evenly distributed among the major HBV genotypes.”

Telbivudine Alone Works as Well as When Combined with Lamivudine

A study, published in the August 2005 issue of *Gastroenterology*, found treatment with just telbivudine was as effective as a combination of telbivudine and lamivudine (EpiVir-HBV).

A randomized, double-blind, multicenter

trial compared the safety and effectiveness of telbivudine alone at two different doses, against lamivudine alone, or a combination of two different doses of telbivudine plus lamivudine in 104 HBeAg-positive adults.

After 52 weeks, the drugs reduced HBV DNA in the following ways:

- With just lamivudine, HBV DNA dropped 4.6-fold.
- With telbivudine at 400 mg daily, the drop was 6.43-fold.
- With telbivudine at 600 mg daily, the drop was 6.09-fold
- The combination of telbivudine at 400 mg plus lamivudine produced a 6.40-fold reduction
- And the combination of telbivudine at 600mg plus lamivudine produced a 6.05-fold decline.

At week 52, telbivudine alone showed a significantly greater reduction in HBV DNA and normalization of ALT levels (86% vs 63% in the lamivudine-only group) and greater HBeAg seroconversion (31% vs 22% in the lamivudine group) and less viral resurgence.

The combination of telbivudine and lamivudine did not produce better results than telbivudine alone. Phase III clinical trials of telbivudine are continuing.

Stopping Lamivudine after HBeAg Seroconversion May Be Good for Some Patients

Doctors have long grappled with when to stop lamivudine treatment in patients who clear HBeAg and produce “e” antibodies to avoid development of viral resistance to the antiviral.

South Korean researchers, writing in the November 2005 issue of the *Journal of Medical Virology*, suggest that stopping lamivudine after seroconversion may be good for a few select patients.

Researchers studied and compared 38 patients who continued lamivudine after seroconversion, with 35 who stopped treatment over one year. They found no difference in the rate of HBV DNA rebound and liver damage in the two groups.

However, six patients in the group that stopped treatment developed severe liver damage. For them, unhealthy bilirubin levels was a predictor of whether liver damage would ensue when treatment stopped.

“This study suggests that discontinuation of lamivudine may be an option in older patients with normal bilirubin level,” they concluded.

Lamivudine Could Be Effective in Patients with Severe Liver Damage

Using antivirals in patients with severe liver damage and scarring (decompensated cirrhosis) has been considered risky. Recently, a team of researchers treated 17 patients for about two years, 12 had Child class B liver damage and five had Child class C.

Writing in the October 2005 *Journal of Gastroenterology and Hepatology*, the researchers reported that 10 of the 17 patients (58.2%) responded well to lamivudine treatment. As expected, six patients developed

viral resistance, but improvement in liver health was observed in nine of 10 patients who responded to the treatment, and six of the patients whose HBV DNA levels rebounded despite treatment.

HBeAg seroconversion was achieved in five of 13 HBeAg-positive patients at the last follow up and during the follow-up period.

“Long-term administration of lamivudine for patients with decompensated cirrhosis is effective,” the researchers asserted. “Earlier lamivudine administration in Child class B patients led to improved clinical outcomes.”

An Endorsement for Pegylated Interferon as First-Line Treatment in Asians

Hong Kong researchers have evaluated pegylated interferon and recommend that a six-month treatment regimen should be “considered as one of the first-line therapeutic options for

hepatitis B virus infection.”

Writing in the September 2005 issue of the journal of *Alimentary Pharmacology and Therapeutics*, the researchers analyzed data from four published studies, three included predominantly Asian patients.

“Peginterferon is found to be superior to lamivudine monotherapy and induced sustained biochemical and virological responses in about one-thirds of patients after 12 months of therapy,” they wrote.

Indian Researchers Find Lamivudine-Interferon Sequential Treatment Beneficial

Indian researchers found 80% of HBeAg-positive patients with elevated ALT levels benefited from sequential therapy with lamivudine and conventional interferon and sustained their good responses, while only 20% of those treated with just lamivudine achieved similar results.

Writing in the *American Journal of Gastroenterology*, the researchers described treating two groups of

75 patients. One group was treated with only lamivudine for 52 weeks. The other was treated with lamivudine for one year, with interferon added for 16 weeks starting at week 8.

At week 52, HBeAg loss occurred in 15 (39.5%) of the group receiving lamivudine and interferon (Group A), and in 14 (37.8%) in those treated with just lamivudine (Group B), meanwhile HBeAg loss, anti-HBe appearance, and undetectable HBV DNA levels were seen in 26.3% and 13.5% respectively.

Nine of 10 (90%) patients in group A and one of five (20%) in group B maintained the response through week 76. At week 76, five additional patients in group A and three in group B achieved HBeAg seroconversion and undetectable HBV DNA.

At week 76, undetectable HBV DNA was seen in 39.5% and 16.2% in groups A and B, respectively. Normal ALT was seen in 47.7% and 40.5% at week 52 and ALT was normal in 39.5% and 13.5% at week 76 in groups A and B, respectively.

“Our results demonstrate that sequential therapy is superior to lamivudine monotherapy in achieving sustained seroconversion, ALT normalization, and HBV DNA loss. Compared to 80% with sequential therapy, only 20% Indian patients with CHB did not relapse after stopping lamivudine monotherapy,” they wrote.

Expert Opinion: How to Treat Hepatitis B and C Coinfections

Two leading Stanford University School of Medicine gastroenterologists, Seth D. Crockett and Emmet B. Keeffe, recently wrote how to treat patients coinfecting with hepatitis B and C. In coinfecting patients, often one virus will become the “dominant” virus.

Once screening for liver health and viral genotype is completed, patients should be treated only if liver damage is occurring. In patients with HCV-dominant disease, pegylated interferon and the antiviral ribavirin are recommended.

In patients with active hepatitis B infections, pegylated interferon

alone or with lamivudine should be considered.

“Additional studies are required before adefovir or entecavir can be recommended in this patient population, but regimens containing these agents may be useful on a case-by-case basis in patients with HBV-dominant disease,” the physicians wrote.

What’s the Best Treatment for Hepatitis B and HIV Coinfected? Tenofovir

Researchers at Johns Hopkins University, writing in the Oct. 1 issue of the journal of *Clinical Infectious Diseases*, advocate the use of the antiviral tenofovir to treat patients coinfecting with hepatitis B and HIV. Tenofovir has not yet been approved by the U.S. Food and Drug Administration for treatment of hepatitis B.

“Clearly, the strength of our recommendation for the use of tenofovir DF would be much

greater if the drug had been licensed for the treatment of chronic hepatitis B, but the use of tenofovir DF is easily justified in light of available data,” the study’s authors contend.

“Furthermore, with the commercial availability of tenofovir DFemtricitabine, a single pill that is part of an HIV regimen can be used for hepatitis B treatment, providing two agents with dual activity against HIV and HBV.”

Until there are better data to support this recommendation, the authors suggest, “The best approach to the treatment of chronic hepatitis B in HIV-infected persons will require thinking “outside the black box,” and in particular, coupling the available data on the treatment of chronic hepatitis B in persons without HIV infection with sound clinical judgment.”

Health Officials Push for Universal Adult Hepatitis B Immunization

Health officials are increasingly calling for

hepatitis B immunization of all adults, and they plan to ask the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (ACIP) to recommend its vaccine for all adults at its next meeting in late October, according to a Sept. 26 report in the *American Medical News*.

Currently, CDC promotes immunization for adults in prison, men who have sex with men and people with multiple sex partners. The change is needed because of the additional time it takes to screen patients for hepatitis B.

“Discussing sensitive lifestyle issues (e.g., hepatitis A and sexual preferences and practices, needle use and other drug use) and reviewing 10 screening questions with one’s patients are not the nation’s possible within the time allotted for a visit to most the physician’s office,” Immunization Action Coalition officials wrote.

In addition, taking a sex history can open a Pandora’s box of sensitive personal issues that may require special training to help patients

sort through, and patients often do not want their risk behaviors recorded in medical records that could be used by insurers.

The Migrant Clinicians Network also urged ACIP to broaden its recommendation. “Basing the need for hepatitis B vaccination on sexual risk also perpetuates the stigma around hepatitis, rather than promoting the necessity of current vaccinations as routine preventive health care,” officials noted.

Some groups said they would like people up to age 40 or 50 to receive the vaccine while others suggest up to age 25. Recent increases in the incidence of hepatitis B among people ages 20 to 39 and even among those older than 40 would suggest that people up to age 50 should be vaccinated, wrote Jeffrey Davis, Wisconsin’s state epidemiologist for communicable diseases.

When the hepatitis B vaccine was introduced, it didn’t have the positive impact that was expected, said Jules Dienstag, professor of medicine at Harvard Medical School. One of the reasons was

that 33% of people with hepatitis B were not in any high-risk group, he said.

Journal Identifies Missed Opportunity to Vaccinate Urban Adults Against HBV

A survey of young adults living in a Brooklyn community investigated how effective hepatitis B immunization and prevention efforts have been in this high drug use neighborhood.

Writing in the September 2005 issue of the *Journal of Urban Health*, researchers say the health system has missed the boat in protecting this population.

Researchers sampled 157 residents and tested them for HBsAg, surface antibodies, and core antibodies, which show past infection. They found evidence of hepatitis B immunization in only 19.6% of study participants.

HBV infection was higher among those who had used crack or injected drugs as well as among those

who had bartered sex for money or drugs. Medicaid coverage was linked to lower infection rates and higher rates of immunization.

“Although adolescent hepatitis B immunization has been a public health priority in the United States since 1995, nearly three-quarters of young adults in this community did not have serological evidence of being either exposed or immunized,” the authors concluded.

HIV Viral Load, Not CD4 Cell Count, Predicts Success of Hepatitis B Vaccine

One out of every six vaccinations in HIV-infected people are effective in producing adequate antibody protection against hepatitis B infection, according to a report in the Oct. 1 issue of the journal of *Clinical Infectious Diseases*.

HBV-HIV coinfection significantly increases the death rate in people with HIV so the search is on for an effective immunization to protect the HIV-infected from hepatitis B.

Researchers recently reported that HIV viral load at the time of the first and third vaccine dose administrations predicted the immunization’s success.

No significant difference in CD4 cell count was found in those who responded well to the vaccine, contradicting an earlier study that suggested that CD4 cell count played a role in the response to the vaccine.

Researchers now say immunization works when the HIV viral load is below 400 copies/ml at the time of vaccination.

Latest Study Undecided about Milk Thistle’s Effectiveness

A major review of studies that examined the effectiveness of the herbal supplement milk thistle in patients with hepatitis B or C and/or alcoholic liver disease found it “does not seem to significantly influence the course of patients with alcoholic and/or hepatitis B or C liver diseases.”

Researchers, writing in the September 2005 issue of the *American Journal of Gastroen-*

terology, assessed the benefit and potential harm from milk thistle by reviewing 13 clinical trials that involved 915 patients with viral hepatitis or alcoholic liver disease.

Death from liver failure was significantly reduced by milk thistle in all trials, they found, but not in scientifically high-quality trials.

In high-caliber trials, the supplement did not “significantly influence the course of patients with alcoholic and/or hepatitis B or C liver diseases.

Researchers pushed for impartial, randomized clinical trials that compared milk thistle to a placebo to investigate the supplement’s true impact on hepatitis B and C.

