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Hepatitis B

What Antivirals Will and Won't Work After Viral Resistance to Lamivudine Develops

Researchers have written an overview on what antivirals will or won't work once viral resistance to the antiviral lamivudine (Epivir-HBV) develops, in the December 2005 issue of the journal of *Antiviral Therapy*.

Working in a lab, researchers assessed the susceptibility of all lamivudine-resistant hepatitis B viruses (HBV), which are able to reproduce despite lamivudine's ability to tamper with their genes, to 11 nucleoside analogues (antivirals) in various stages of clinical development.

Researchers report that lamivudine-resistant HBV remains sensitive to:

- Adefovir (Hepsera, approved by the U.S. Food and Drug Administration)
- Tenofovir and
- Alamifovir

The lamivudine-resistant HBVs have reduced susceptibility to entecavir (Baraclude, also approved by the FDA).

However, these HBVs appear able to resist the antiviral effects of all L-nucleosides tested, including emtricitabine (Emtriva), telbivudine, clevudine, and torcitabine.

Cambodian Survey Finds 15 of 794 Infected People Have HBsAg Mutations

Researchers analyzed blood samples from 794 hepatitis B surface antigen (HBsAg) positive Cambodians to identify what genotype (strain of hepatitis B virus) was dominant in the country, and to test for any significant viral mutations.

Reporting in the January 2006 issue of *Journal of Viral Hepatitis*, researchers reported that the most dominant genotype was C, followed by genotype B. Of the 794 samples, 15 contained mutations in the virus' surface protein (HBsAg). A conventional lab test for HBsAg in blood can fail to identify hepatitis B infection if the genetic make-up of HBsAg is different due to mutations.

Genetic Tendency to Liver Cancer Found in Shared Chromosome

A group of Taiwanese researchers, writing in the January 2006 issue

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of *Oncogenomics*, have found a common chromosome or genetic similarity among Taiwanese families who all have hepatitis B-related liver cancer.

The researchers identified a common chromosome or gene that appears susceptible to liver cancer. They studied 191 families and found some shared a common genetic predisposition to liver cancer within their chromosomes.

Sexuality and Drug Use Define Which Hepatitis Infects HIV-Hepatitis Coinfected

Writing in the January 2006 issue of the *Journal of Hepatology*, a researcher from the U.S. Centers for Disease Control and Prevention (CDC) explored the epidemiology of viral hepatitis and HIV coinfection in the United States.

Worldwide, there are an estimated 370 million chronic HBV infections, 130 million hepatitis C virus (HCV) infections and 40 million HIV infections. About 2-4 million with HIV also have HBV infections.

While HBV, HCV and HIV share common routes of transmission – sexual, injecting drug use and mother-to-child – the number of coinfected differ based on their sexual orientation and drug use practices.

"Among HIV-positive persons studied from Western Europe and the USA, chronic HBV infection has been found in 6 to 14% overall, including 4 to 6% of heterosexuals, 9 to 17% of men who have sex with men (MSM), and 7 to 10% of injection drug users," the researcher wrote. "HCV infection has been found in 25-30% of HIV-positive persons overall; 72-95% of injection drug users, 1-12% of MSM and 9-27% of heterosexuals."

The characteristics of HIV and hepatitis coinfected people can change, based on their coinfecting hepatitis virus and their epidemiologic profile. "[S]urveillance systems are needed to monitor their infection patterns in order to ensure that prevention measures are targeted appropriately," the researcher recommended.

Doctors Warned About Possible Liver Damage from the Antibiotic Ketek

Two cases of liver failure and one case of liver damage and inflammation have been linked to the antibiotic Ketek (Telithromycin), according to a report from an upcoming issue of the *Annals of Internal Medicine*.

Carolinas Medical Center researchers, based in Charlotte, N.C., report one of the patients died; one required and received a liver transplant; and the third recovered from drug-induced hepatitis after the antibiotic was stopped. None of the three had prior liver infection or problems.

"These cases could represent an unusual clustering of a rare, idiosyncratic drug reaction at one medical center," said John S. Hanson, MD, an author and hepatologist with the liver transplant center at Carolinas Medical Center. "However, the severity of liver injury in two of our patients warrants this report in the medical literature and will alert other physicians to this possible link with telithromycin."

The FDA approved Telithromycin in 2004 to treat acute bacterial infections including chronic bronchitis, acute bacterial sinusitis and community-acquired pneumonia.

Patients with hepatitis B should not take this antibiotic until additional investigations are performed.

The reports do not prove that the antibiotic caused the liver damage, but researchers advise "caution in prescribing this drug pending further postmarketing surveillance data."

U.S. Liver Cancer Death Rates Increasing Due to HBV and HCV

The January 2006 issue of *Drug & Market Development Newsletter* reported that while deaths from cancer dropped 1.1% per year between 1993 and 2002, liver cancer deaths increased 3% among white men, 4.5% among black men, 3.7% among white women, and 5% among Hispanic women each year.

While liver cancer is the 20th most common type of cancer in the United States, it ranks 8th in causing cancer

death because doctors often fail to diagnose it until too late.

HCV causes at least half of liver cancer cases in the U.S. However, the large number of people infected with HCV, HBV, or both in the U.S. is expected to increase liver cancer rates during the next two decades.

The incidence of new HBV infections has dropped dramatically – from about 21,000 per year in 1990 to fewer than 8,000 in 2005. However, the prevalence of existing chronic infections remain high, predisposing many people to liver cancer after decades of infection. HBV causes liver cancer by integrating into normal liver cell DNA. Cirrhosis (scarring of the liver) then occurs, and cell mutations leading to malignant cell growth may occur as the liver attempts to regenerate itself. An estimated 5% of people with cirrhosis develop liver cancer.

Faced with Organ Shortage, Doctors Successfully Transplant HBsAg-Infected Liver

Faced with a severe shortage of donor liver organs, a team of British Columbia doctors successfully transplanted an HBV-infected donor liver in a patient who was experiencing severe liver damage due to HBV and HCV coinfection.

To date, physicians have tried to avoid using donor organs already infected with viral hepatitis. In this case, the HBsAg-positive liver was transplanted in a 26-year-old man. His HBV DNA (viral load) increased after the transplantation, despite treatment with the antiviral lamivudine (Epivir-HBV), however it became undetectable after treatment with the antiviral adefovir (Hepsera).

Five months after the operation, his liver enzymes, which indicate liver cell damage or death, began to rise due to a return of HCV infection. Treatment with pegylated interferon and ribavirin (an antiviral used to treat hepatitis C) successfully cleared HCV RNA.

Two years after the transplant, the patient is healthy, despite the presence of HBsAg. "Our experience suggests that with effective antiviral therapy, the use of HBsAg seropositive donors is feasible in selected circumstances," wrote the researchers in their report published in the January 2006 issue of *Transplantation*.

Patient Dies After Brief Stint on Lamivudine, Doctors Find HBsAg Mutations

A team of German doctors reported on a unique case of a man who was treated for four months with lamivudine. He discontinued treatment on his own after he developed surface antibodies, which normally might indicate he had cleared the virus. However, he died from liver failure shortly thereafter.

Writing in the January 2006 issue of the *Journal of Medical Virology*, the doctors report that apparently after stopping the antiviral, his viral load increased dramatically, despite the appearance of the surface antibody.

When doctors examined the molecular make-up of his HBV, they found he had developed a mutation in the surface protein, so though he appeared to clear the virus, the HBV continued in its mutated form.

"HBV replication resumed after the uncontrolled cessation of lamivudine treatment in this patient and may have triggered the process leading to liver failure," researchers wrote.

Among Elderly, Liver Cancer Treatment is Poor and Inconsistent Across the U.S.

A study of America's Medicare population (age 65 and older), found there was inconsistent care to elderly patients with liver cancer, according to a report published in the January 2006 issue of *Hepatology*.

The team of researchers noted that different approaches to treatment geographically was one reason treatment was so varied and often substandard.

"More importantly, only a third of patients with favorable tumor features who were most likely to benefit received such therapy," they noted. "Second, potentially inappropriate use of curative ther-

apy, mostly resection (surgery), was observed in approximately a fifth of patients with unfavorable features such as lesions. Lastly, there were remarkable geographic variations indicative of wide practice variations in the extent and type of curative, as well as palliative, therapies."

The SEER-Medicare dataset contains Medicare claims data dating back to 1991 for all Medicare-enrolled patients identified by SEER registries between 1992 and 1999. SEER collects population-based cancer incidence and survival data on incident cancer cases from 11 population-based cancer registries that account for 14% of the population in the United States.

JAMA Study Confirms High Viral Load Carries High Risk of Liver Cancer

People with high viral load are at increased risk of developing liver cancer, no matter what their "e" antigen (HBeAg) status is, according to a report published in *The Journal of the American Medical Association*, conducted by the R.E.V.E.A.L.-HBV Study (Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-HBV Study).

The study evaluated the relationship between HBV and liver cancer in 3,653 people between 1991 and 2004 in Taiwan.

The study found that liver cancer risk was two times higher when viral load reached or exceeded 10,000 copies/mL, compared to patients with undetectable HBV DNA.

The study also found that patients with persistently elevated HBV DNA (greater than or equal to 100,000 copies/mL) over the years had a greater than five times risk for liver cancer, compared to patients with lower HBV DNA levels.

HBV-Related Liver Cancer More Aggressive than HCV-Related Liver Cancer

A report published in the January 2006 issue of *The American Journal of Gastroenterology* found that HBV-related liver cancer has a "greater aggressiveness" than hepatitis C virus-related tumors.

The researchers compared 102 pairs of patients with either HBV- or HCV-related liver cancer. Patients were matched for sex, age, residence, underlying chronic liver infection, cirrhosis and stage of cancer.

They found that HBV-infected patients tended to have a poor prognosis than those with hepatitis C. This difference became more profound as cancer advanced with time.

HIV Antiviral Emtricitabine Effective Against HBV in Global Double-Blind Study

Researchers conducted a randomized, double-blind study of the effectiveness of the antiviral emtricitabine (previously used to treat only HIV), in HBV-infected patients in North America, Asia and Europe.

Doctors treated 167 patients with 200 mg of emtricitabine and 81 patients with placebo for 48 weeks, and then all patients underwent a liver biopsy.

Sixty-two percent of the 167 treated patients had improved liver health, compared to 25% in the placebo group, and 54% of the emtricitabine-treated patients had low viral load (less than 400 copies/mL) compared to 2% in the placebo group.

"At week 48, 13% of 159 patients in the emtricitabine group with HBV DNA measured at the end of treatment had detectable virus with resistance mutations (95% confidence interval)," researchers reported in the Jan. 9, 2006 issue of the *Archives of Internal Medicine*.

The rate of HBeAg loss and development of the "e" antibody was the same between the two groups. As with most antiviral treatment, HBV infection rebounded in 23% of emtricitabine-treated patients once treatment stopped.

Doctors concluded that in "patients with chronic HBV, both positive and negative for HBe antigen, 48 weeks of emtricitabine treatment resulted in significant histologic, virologic, and biochemical improvement."

Dr. Anna S. Lok from University of Michigan Medical Center in Ann Arbor, and co-author

Dr. Stephen N. Wong, commented that "with the advent of newer antiviral agents with significantly lower risk of resistance, emtricitabine on its own will not have a role in the treatment of hepatitis B. Whether the combination of emtricitabine and tenofovir is superior to other approved treatments for hepatitis B remains to be determined."

Case Study: Antiviral Tenofovir Succeeds When Adefovir Resistance Develops

Writing in the January 2006 issue of *Comparative Hepatology*, doctors report using the experimental antiviral tenofovir to treat a cirrhotic HBV patient who had developed viral resistance to the antiviral adefovir (Hepsera).

The patient had initially developed resistance to lamivudine and had been switched to adefovir two years earlier. However, his viral load and liver health did not improve during the adefovir treatment and doctors discovered his HBV had developed resistance to the drug.

Doctors successfully treated the patient with tenofovir (an antiviral not yet approved by FDA for treatment of hepatitis B), which appears to be an effective against adefovir-resistant HBV.

They wrote: "Incomplete control of viral replication with adefovir requires monitoring for viral resistance and should prompt a change in antiviral treatment."

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