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Hepatitis B

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When Lamivudine Resistance Occurs, Continue Lamivudine and Add Adefovir

Greek researchers studied which treatment regimen is better for patients infected with the hepatitis B virus (HBV) that can “resist” or continue to replicate despite treatment with the antiviral lamivudine (EpiVir-HBV).

Antivirals such as lamivudine work by disabling HBV’s genetic material, but over time, some HBV with special mutations can continue to replicate despite the antiviral and soon the infection rebounds.

Researchers wanted to know if resistant patients who did not have the hepatitis B “e” antigen (HBeAg-negative), fared better if lamivudine was dropped completely and replaced with the antiviral adefovir (Hepsera), or if they did better if adefovir

was added to the ongoing lamivudine treatment.

Writing in the January 2007 issue of *Hepatology*, they reported that 14 patients were switched to only adefovir and 28 had adefovir added to their ongoing lamivudine treatment. Within 12 months, HBV DNA (viral load) became undetectable and alanine aminotransferase (ALT) levels became normal in 71% of adefovir-only patients and in 90% of the adefovir and lamivudine group. Elevated ALT levels indicate liver cell damage or death.

Patients who started with moderate or low HBV DNA levels experienced an earlier decline in HBV DNA, compared with patients with higher viral loads.

Researchers reported that three (21%) adefovir-only patients experienced a rebound in viral load and ALT levels due to adefovir

resistance after 15 to 18 months of treatment.

“Adding adefovir to lamivudine in HBeAg-negative patients with lamivudine resistance effectively suppresses HBV replication in most of them and induces biochemical remission that can be maintained in all of them at least for three years without any evidence of development of resistance to adefovir,” they wrote.

Risk of Cirrhosis Increases at Age 40 in HBeAg-Positive Patients

Researchers followed a group of HBV-infected people who had been infected since birth to see what impact HBeAg seroconversion (loss of the “e” antigen and development of the “e” antibody) had on the health of their livers.

Often, people infected at birth experience three in-

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fection stages: immune tolerance during which time the immune system does not notice or attack the infection, immune clearance when the immune system actively attacks HBV-infected liver cells, and then asymptomatic infection, when viral load and liver damage is minimal and patients are HBeAg-negative.

Usually, by age 40, nearly 90% of HBV-infected people will have moved through the first two phases and become HBeAg negative.

Researchers, writing in the *Journal of Viral Hepatitis*, reported that patients age 40 and older who still had HBeAg had a high risk of liver damage and severe scarring (cirrhosis). These patients with “delayed” HBeAg seroconversion should therefore be treated with either interferon or antivirals, the researchers recommend, to prevent liver damage.

Surprisingly, Young Liver Cancer Patients Have Relatively Low Viral Loads

Taiwanese researchers studied what role viral load (HBV DNA – the amount of virus in the bloodstream) played in the development of liver cancer in young people

younger than age 40, compared to older patients with liver cancer.

They monitored 183 HBV-related liver cancer patients and 202 HBV-infected patients and compared viral loads and ALT levels.

Writing in the March 2007 issue of the *Journal of Viral Hepatitis*, they reported that HBV DNA levels were lower in young cancer patients than among older cancer patients.

However, young cancer patients with HBV genotype B had higher viral loads than those with genotype C. While high HBV DNA levels were associated with the development of liver cancer in older patients, it appeared not to be a risk factor in younger patients.

Researchers concluded that, “viral factors in association with the development of HBV-related liver cancer in young patients may be different from their older counterparts. The complicated interplay between host and virus could be responsible for the emergence and aggressive outcome of early-onset liver cancer.”

Mutations in Surface Antigen Cause High Viral Load and Severe Liver Disease

A team of South Korean researchers studied the impact of mutations in the surface antigen (called pre-S mutations) in people with HBV genotype C infections. Experts are beginning to examine what role these mutations play in the progression of HBV infection.

They studied 300 patients, including 91 with cirrhosis and 72 with liver cancer.

Pre-S mutations were detected in 82 patients (27.3%), and they were found more frequently in liver cancer patients (43.1%) and patients with cirrhosis (35.2%) than in asymptomatic HBV-infected people.

The surface mutations were also more common in older patients and those with high viral loads.

“These findings suggest that pre-S mutations... are common in patients with genotype C HBV infection and are associated with advanced liver disease and active viral replication,” they wrote in the March 2007 issue of the *Journal of Viral Hepatitis*.

Patients Who Lose HBsAg During Lamivudine Treatment May Still Harbor HBV DNA

When patients who are treated with lamivudine lose the surface antigen, have they really totally eradicated the virus? Taiwanese researchers examined the authenticity of this “cure” in 11 patients who cleared HBsAg during lamivudine treatment.

According to their report in *Gastroenterology*, HBV DNA was still detectable in the patients’ blood samples, despite the loss of HBsAg. The researchers discovered that a mutation in the surface antigen had altered its make-up enough so it evaded detection by laboratory tests.

Researchers warned doctors that HBV DNA levels should be checked in all patients who lose HBV DNA during lamivudine treatment. “... It may be caused by a point mutation in the S gene, which results in detection failure,” they wrote. “In such patients, further verification and follow-up using a sensitive HBV-DNA test are advised.”

Researchers Find Many Men with Normal ALTs Have HBV DNA But No HBsAg

South Korean researchers investigated how prevalent “occult” HBV infection – when HBsAg is undetectable but HBV DNA is detectable – was among people with normal ALT levels. They collected blood samples from 195 people with a history of alcohol abuse and normal ALT levels. All tested negative for HBsAg.

Surprisingly, HBV DNA was detected in 31 of 195 subjects (16%). Prevalence of occult hepatitis B was significantly higher in the men (23%) than in women (8%).

The researchers, writing in the February 2007 issue of the *Journal of Infection*, encouraged physicians to be “meticulous” about testing HBV DNA, and not just HBsAg, when selecting blood or organ donors.

Core Antigen Mutations Also Impact HBeAg Seroconversion and Disease Progression

South Korean researchers studied the impact of one or more

core promoter (CP) mutations, located in the core antigen of the virus, on HBeAg seroconversion and disease progression. They followed 29 HBeAg-positive patients for more than 12 years. All patients had HBV genotype C, and none had cirrhosis at the start of the study.

They reported in the March issue of the *Journal of Viral Hepatitis* that patients without double core promoter mutations achieved earlier HBeAg seroconversion than those with core mutations (6.9 vs 9.4 years).

Those with double CP mutations experienced a higher rate of cirrhosis and liver cancer than those without mutations.

The researchers concluded that the core mutations are significantly related to, “liver deterioration in HBeAg-positive genotype C active hepatitis patients. A longer period of immune clearance coupled with delayed HBeAg seroconversion appears to contribute to disease progression in patients harbouring these mutations in the CP region of HBV.”

Simultaneous Treatment with Lamivudine and Tenofovir Best for HIV-HBV Co-infected

A researcher at the University of Texas Southwestern Medical Center at Dallas treated 45 people co-infected with HBV and HIV with three different treatment regimens to see which worked best.

Fifteen received just lamivudine, 10 receive lamivudine and tenofovir – an antiviral that has not yet been approved by the U.S. Food and Drug Administration (FDA) for hepatitis B treatment, and 20 received lamivudine, followed by the addition of tenofovir.

More patients treated simultaneously with lamivudine and tenofovir achieved undetectable HBV DNA and lost HBeAg than did patients in the other two groups, according to the researchers’ report in the March issue of the *Journal of Viral Hepatitis*.

More patients with HBV genotype A achieved undetectable HBV DNA than patients with non-A genotypes (74% vs 20%), regardless of their treatment regimen.

Lamivudine Treatment after Liver Tumor Removal Improves Survival

Japanese researchers compared survival and recurrence of liver tumors in two groups of HBV-infected patients with high HBV DNA levels. Fourteen patients were treated with lamivudine after surgery, according to the report in the February 2007 issue of *Hepatitis Research: the official journal of the Japan Society of Hepatology*, and 10 patients received no antiviral treatment.

Tumor-free survival rates after surgery was significantly higher in the lamivudine-treated group. The absence of lamivudine therapy and having more than one tumor also increased the risk of tumor recurrence.

Four patients developed lamivudine resistance, and two were then treated with the antiviral adefovir due to increases in ALT levels. While lamivudine improved the health of surgery patients, researchers cautioned doctors to carefully monitor patients for lamivudine-resistance to prevent a dangerous rebound in ALT levels.

Higher Adefovir Dose Needed in HBeAg-Positive Patients with Lamivudine Resistance

The FDA-approved dose for adefovir is 10 mg daily, but French researchers found that some lamivudine-resistant, HBeAg-positive patients failed to respond to this dose.

According to their report in the February 2007 issue of the *Journal of Hepatology*, they tried 20 mg daily in five patients and found no ill effects on patients' kidneys and no increased rate of viral resistance to adefovir. Viral load dropped, and ALT levels normalized in all but one patient.

"These results suggest: (i) that suboptimal responses to adefovir 10mg daily are due to under dosing; and (ii) that increasing the adefovir dose to 20mg daily is beneficial and safe in patients with lamivudine-resistant HBV (who have a) suboptimal response to adefovir 10 mg daily," researchers wrote.

One-Quarter of HBsAg-positive Blood Donors with Undetectable HBV DNA Have Liver Damage

A study, published in the February 2007 issue of the

Journal of Clinical Gastroenterology, found that some people with very low levels of HBV DNA still have liver damage, despite the seemingly asymptomatic status of their infection.

The researchers screened 78 blood donors with HBsAg and identified 47 with detectable HBV DNA. ALT levels were elevated in 26, and 31 of the patients were HBeAg negative. Liver biopsies were performed on all of the patients.

As expected, patients with elevated viral loads and ALT levels had signs of liver fibrosis and cirrhosis. But what surprised researchers was that 25% of the patients who had undetectable HBV DNA still had liver damage resulting from their HBV infection.

Half of HBeAg-Negative Patients Respond to Interferon, One-Third Sustain Response Five Years Later

A team of Turkish researchers evaluated the long-term effects of conventional interferon treatment in 80 HBeAg-negative patients, (mostly men, average age 40) over 60 months to see how successful the treatment had been.

Writing in the January 2007 issue of *Digestive Diseases and Sciences*, the researchers reported that at the end of six months of interferon treatment, 44 (55%) of the patients had undetectable HBV DNA and normal ALT levels.

After nearly five years, 27 patients (61.4%) showed a rebound in ALT and HBV DNA (63% in first year). Recurrence of HBV DNA was not detected until two years after treatment ended. Improvement in liver health was noted in 83.3% patients and HBsAg became negative in four patients (5%).

Researchers concluded that the younger the patient, the better their results. "Nearly half of the patients with HBeAg-negative hepatitis B responds to interferon at the end of therapy," they wrote. "Despite the high recurrence rates, response continues in about one third of patients after a mean of 59.5 months."

Hepatitis B Vaccine Boosters May Not Confer Additional Protection

Italian researchers followed 620 adolescents who had been vaccinated against hepatitis B in 1992 for 11 years to see how effective the vaccine was

over time. They measured the quantity of hepatitis B surface antibodies in 480 of the children one month after vaccination, and then retested the children in 1999 and in 2003.

Writing in a recent issue of *Vaccine*, they reported that after initial immunization, individuals with surface antibody levels higher than 10 mIU/ml were considered adequately protected. Those with lower levels of antibodies were given a vaccine booster and retested.

In 2003, 208 of 228 (91.2%) vaccinees retained protective antibody concentrations and none tested positive for the hepatitis B core antibody, which indicates a past infection. Of the 12 that were given boosters, 11 (91.7%) showed a vigorous response with elevated levels of antibodies, while one child showed a weak response.

"These data suggests that hepatitis B vaccination can confer long-term immunity and that immunological memory can outlast the loss of antibody," researchers wrote. "Hence, the use of routine booster doses of vaccine does not appear necessary to maintain long-term protection in successfully vaccinated immunocompetent individuals."

