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Hepatitis B

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Pegylated Interferon Continues to Show Success against HBV

According to a report in the Jan. 8, 2005 issue of *The Lancet*, about one-third of patients chronically infected with the hepatitis B virus (HBV) clear the "e" antigen (HBeAg) when treated with pegylated interferon alfa-2b (Schering-Plough's PegIntron).

However, when the antiviral lamivudine (Epivir-HBV) is added to the interferon treatment, no additional benefits are achieved.

German researchers gave 166 patients either the two-drug combination in weekly doses of

PegIntron (100 mg) and daily lamivudine (100 mg), or just PegIntron. The PegIntron dose was lowered to 50 mg per week after 32 weeks.

At the end of week 52, HBeAg loss was in 44% in the combination group and 29% in the group receiving only interferon. At the end of follow-up (week 78) period, sustained HBeAg loss was 35% in and 36% respectively.

At week 52, HBV DNA suppression was below 200,000 copies per mL in 74% of the combination group, compared to 29% in the interferon group. At week 78 it was 32% vs. 27% respectively.

Sustained HBeAg varied with HBV genotype, genotype A had a

47% undetectable rate and B had 44% rate. Genotype C had a 28% rate and D had a 25% undetectable rate.

Clearance of HBeAg and reduction of viral load was as high or higher than with any other therapy reported, the authors concluded.

Vaccine Plus Lamivudine Results in a 56% HBeAg Seroconversion Rate

Using a hepatitis B vaccine therapeutically to fight chronic hepatitis B has been unsuccessful to date, but recently Japanese researchers tried combining the vaccine with the

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antiviral lamivudine, which prevents HBV from replicating by tempering with its genetic material.

Researchers hoped the antiviral would lower the viral load by inhibiting viral replication, and the vaccine would spur the immune system to fight the infection on its own.

Researchers followed 72 patients (40 were HBeAg positive and 32 had the “e” antibody (anti-HBe). All patients received lamivudine for 12 months. Nine of the HBeAg patients and six anti-HBe patients were also given a vaccine containing 20 mug of hepatitis B surface antigen (HBsAg) once every two weeks for 12 total vaccine injections.

Twelve months after the start of therapy, HBV DNA became negative in all nine of the HBeAg patients receiving lamivudine and the vaccine, and in 15 of 31 (48%) who received only lamivudine.

The rate of seroconversion from HBeAg to anti-HBe was higher in patients receiving combination therapy (56%) compared to those receiving just lamivudine (16%).

Of the 57 patients receiving only lamivudine, HBV DNA rebounded in 10, due probably to development of HBV with mutations that could replicate despite lamivudine’s antiviral effects. None receiving combination therapy experienced a viral rebound or “break-through.”

“Combination therapy represents a better therapeutic regimen with few complications in patients with chronic hepatitis B,” the researchers reported in the February 2005 issue of the *Journal of Clinical Virology*.

African-American HBV Infection Rate Three Times That of White Americans

An article in the February 2005 issue of the *Journal of Clinical Gastroenterology* comparing HBV infection rates between White Americans, African-Americans, Hispanic Americans and Native Americans found dis-

turbing disparities between majority and minority populations, despite advances in vaccination and treatment.

While childhood immunizations against hepatitis B have been available for more than a decade, African-Americans remain three times more likely to contract acute hepatitis B than Whites, and the prevalence of HBV infections remained significantly higher in African-Americans (11.9%) than in Whites (2.6%).

Among high-risk groups, including those coinfecting with hepatitis C and veterans with severe mental illness, African-American infection rates ranged from 28% to 75%, compared to Whites’ infection rates of 12% to 20%.

The reported infection rate among Hispanic Americans remains slightly higher than in Whites. HBV prevalence has only been evaluated in a sub-population of Mexican-Americans, which found a slightly higher rate than estimated in Whites (4.4% vs. 2.6%).

Infection rates in other Hispanic-American groups, such as mainland Puerto Ricans, Cuban-Americans, and Spanish-speaking Caribbean, Central and South American communities were not available.

HBV infection rates among Native Americans remain twice as high as in White Americans, according to studies of Alaskan and mainland tribal people. Specific data by tribe or clan was not available.

Americans of Asian or Pacific Islander descent were not included in the report.

55% of Adults with Liver Disease Have Been Infected with Hepatitis A

A study of past hepatitis A viral (HAV) infections among 454 adults with chronic liver disease resulting from alcohol abuse or HBV or hepatitis C virus (HCV) infec-

tion, found that older age, ethnic origin and history of alcohol abuse increased hepatitis A exposure.

Hepatitis A is a short-lived (acute) infection of the liver. While HAV rarely causes death, the addition of another viral infection in the liver can worsen or accelerate liver damage in those with existing viral hepatitis infections.

According to a report published in the January 2005 issue of the *Journal of Viral Hepatology*, HCV, HBV, alcohol, and a combination of HCV and alcohol were the causes of liver disease in 337, 72, 37 and eight patients, respectively. The overall HAV exposure rate was 55%. The HAV prevalence for ages 21-30, 31-40, 41-50, 51-60, 61-70 and greater than 70 years was 44, 51, 44, 63, 65 and 64%, respectively. Hispanic ethnicity, Asian ethnicity, alcohol abuse and those in the 51-70 age group were at highest risk of HAV exposure.

Chemotherapy Heightens Risk of Liver Damage in HBV-Infected Cancer Patients

Writing in the February 2005 issue of the *European Journal of Haematology*, a team of Japanese researchers reported finding a higher rate of liver damage among HBV-infected patients who received chemotherapy treatment for cancer, than among hepatitis C-infected patients.

They studied 601 adult patients who were treated with chemotherapy for leukemia, lymphomas and myelomas. Of the patients, 7.3% were infected with HBV and 10.1% had hepatitis C. After treatment ended, the rate of liver injury was 36% among HBV-infected, 10.8% among hepatitis C-infected patients, and 12.6% in patients without viral hepatitis.

“After lamivudine became available in our institution, the incidence of liver injury in HBV carriers was reduced to 10%,” the researchers reported. “The therapeutic strategy for hematological malignancies in hepatitis virus carriers should be further investigated.”

Low-Dose HBIG and High-Dose Lamivudine Prevents HBV After Transplantation

Today, Hepatitis B Immune Globulin (HBIG or surface antibodies) and the antiviral lamivudine are used together to prevent recurrence of hepatitis B after liver transplantation, but the dosage and treatment duration of these drugs have not been established.

Turkish researchers tested high doses of lamivudine (300 mg/day) in combination with low doses of very costly HBIG (200-400 IU/2-4 weeks) in 80 transplant patients. Twenty had hepatitis D virus co-infection and eight were HBV DNA-positive at the time of their transplants.

Recurrence of hepatitis B surface antigen (HBsAg) occurred in only three out of 78 (4%) patients; two of the three had been HBV DNA-positive before their liver transplants.

Writing in the Decem-

ber 2004 issue of the *Journal of Antiviral Therapy*, the researchers concluded, “... a combination of lamivudine 300 mg/day and low-dose HBIG prevents post-transplantation recurrence of hepatitis B, even in the presence of viral replication in the pre-transplant period.”

Coffee and Caffeine Reduce ALT Levels in Those with Liver Damage

The National Institute of Diabetes and Digestive and Kidney Diseases recently investigated whether coffee and caffeine consumption reduced the risk of elevated alanine aminotransferase (ALT) levels in 5,944 adults with liver disease caused by alcohol abuse or viral hepatitis.

Liver cells release ALT into the bloodstream when they are damaged or die.

Elevated ALT levels were found in 8.7% of this high-risk population. Lower ALT levels were found in the

adults who drank more than two cups of either coffee or caffeine-laden beverages daily, compared to those who avoided caffeine, according to the report published in the January 2005 issue of *Gastroenterology*.

Tenofovir May Cause Mild Kidney Dysfunction

Tenofovir (Viread), an antiviral first developed to treat HIV, has been found to be effective against hepatitis B. Recently, a German study published in Jan. 3, 2005, edition of *AIDS* reported the drug could make the kidneys more vulnerable to side-effects from other drugs that stress the kidneys.

Tenofovir is a compound very similar to adefovir, another antiviral medication originally developed to treat HIV. However, at the high doses needed to treat HIV, adefovir was found to cause kidney damage. It is now used at a lower dose to treat hepatitis B.

Clinical trials of tenofovir to treat HIV did not find a high incidence of kidney damage, however, since the drug's approval there have been anecdotal reports of kidney dysfunction in people taking tenofovir, although investigators found in many cases that pre-existing kidney problems were the present before tenofovir was used.

In their study, the German investigators looked specifically at how well creatine and protein was filtered out of urine. Patients taking tenofovir had lower creatine clearance in their urine and also had more protein.

Researchers noted, however, that the kidney dysfunction was mild. Although impaired, the creatine filtration rate was still within normal range.

“Treatment with tenofovir may induce mild renal dysfunction in a higher proportion of patients compared with patients never treated with tenofovir,” researchers noted. Tenofovir may make a kidney more vulnerable to drugs that could stress the kidneys, they added.

Genotype C Incurs Higher HBV DNA Levels with Lamivudine Resistance

Chinese researchers followed 247 patients treated with lamivudine in Guangdong to determine when lamivudine-resistant HBV emerged to boost viral load (HBV DNA) and spur a rise in ALT levels. The patients had either genotype B or C.

Writing in the *Journal of Medical Virology*, the researchers reported that detection of the lamivudine-resistant HBV (called YMDD mutant) precedes HBV-DNA resurgence or breakthrough and a sudden rise in ALT levels, called a flare, in about two to three months.

The ALT flare after the appearance of YMDD mutants was more evident in HBeAg-positive patients than HBeAg-negative patients. The HBV-DNA level was significantly higher in genotype C patients compared with genotype B patients.

“Our result suggest that genotypic monitoring of (the) YMDD mutant is important for the management of patients treated with lamivudine,” the researchers reported.

HBV with Precore Mutations Replicate Rapidly and Cause More Damage

Researchers examined in detail the mutations that occur in the precore section of the virus to determine why these HBV cause more serious liver damage than HBV without mutations. Because of the weak genetic “blueprint” that controls HBV replication, these precore mutations often develop over time in chronically-infected people.

Writing in the January 2005 issue of the *International Journal of Medical*

Science, researchers described decades of HBV infection in a person as equivalent to 1 million years of human evolution.

As the immune system creates antibodies to combat HBeAg, some HBV with precore mutations evade these antibodies because they contain or secrete low levels of HBeAg. Over time, these HBV quickly increase in number and HBV DNA levels rapidly rise and liver damage occurs.

There are several types of mutations in the precore region of the virus that allow for decreased HBeAg levels, researchers pointed out. All of these mutations appear capable of causing rapid liver damage and cancer more rapidly than HBV without precore mutations.

In addition to being more virulent, these HBV, “were found to replicate at up to 10-fold higher levels,” in the liver than normal HBV.

Monitoring HBV DNA After Interferon Treatment Could Predict Liver Cancer

Researchers monitored HBV DNA levels in 57 cirrhotic patients, who had been treated with conventional interferon between 1986 and 1990, for liver cancer.

Twenty-five patients had achieved undetectable HBV DNA either during or after treatment, nine experienced a temporary loss of HBV-DNA, and the remaining 23 retained HBV DNA during and after therapy.

Liver cancer, according to a report in the *Journal of Gastroenterology and Hepatology*, developed in two (8%) of the 25 patients who lost HBV DNA, and in 11 (34.4%) of the 32 patients who retained detectable HBV DNA.

The researchers concluded that a significant drop in viral load could prevent development of liver cancer and urged doctors to continue monitoring patients’ HBV DNA

after treatment to aid in the early detection of liver cancer and tumors.

Childhood and Adult Hepatitis B Vaccine Recommendations Under Review

The hepatitis B working group of the U.S. Advisory Committee on Immunization Practices is developing new immunization recommendations, the first such update since 1991.

The 1991 guidelines recommend screening pregnant women for HBV, providing vaccine and HBIG to infants born to HBV-infected mothers, providing universal infant vaccination, catch-up vaccination of all children and adolescents younger than age 19, and vaccination of adults at high risk of hepatitis B due to injecting drug or sexual practices.

While progress has been made, today not all infants are immunized and many school students and high-risk adults remain unvaccinated.

The new proposal recommends ensuring the screening and reporting of infected women, and administration of the vaccine at birth as part of routine care for all healthy infants. A vote on the changes is scheduled for the February meeting of ACIP.

More Insights into HBV Genotype Response to Treatment

There are eight HBV genotypes or strains (labeled A-H), which are defined by their genetic make-up and the region where they originated. The two most common genotypes worldwide are B and C.

People infected with B and C genotypes tend to experience a long infection period of HBeAg, which results in high viral load over many years. In Asia, liver damage is more severe in carriers of genotype C than B. Those with genotype B tend to respond better to interferon and lamivudine than those with genotype C.

Response to treatment may differ, however, in patients infected with HBV of the same genotype. For example, the response to lamivudine is poorer in patients infected with subtype Ba, which contains a recombination with genotype C, than in those with subtype Bj without such a recombination.

Writing in the 2004 issue of the *Journal of Antimicrobial Chemotherapy*, Japanese researchers conclude, "Influence of genotypes on therapeutic response needs to be examined in patients infected with the other genotypes, particularly in those with genotype A or D infection."

Lamivudine Performs Well in HBV-Infected Dialysis Patients

HBV-infected patients who are treated with lamivudine during dialysis experience similar HBeAg seroconversion rates and development of lamivudine-resistant HBV at the same rate as the general HBV-infected population.

Researchers, reporting in January 2005 issue of the *World Journal of Gastroenterology*, followed 91 HBV-infected patients, seven of whom had kidney transplants and 16 required dialysis. The remainder had normal kidney functions. All were treated for 12 months with lamivudine.

Elimination of HBV DNA occurred in 56% of patients undergoing dialysis and in 53% of patients with normal kidney function. Only one of the seven transplanted patients cleared HBV DNA.

HBeAg was cleared in 36% of dialysis patients, 51% patients with normal kidney function and 43% of transplanted patients. Among patients undergoing dialysis, none developed lamivudine-resistant HBV, however nine patients (13%) with normal kidney function developed resistance and two (29%) of transplanted patients developed viral resistance to the antiviral.

The writers conclude that lamivudine is as effective in dialysis patients as patients with normal kidney function, but transplanted patients face a higher rate of lamivudine resistance.

Doctors Must Carefully Monitor Patients for Interferon-Related Depression

Writing in the January 2005 issue of the *Journal of Psychopharmacology*, researchers urged doctor to closely monitor hepatitis C patients for signs of depression when treating them with interferon.

Hepatitis B patients are also treated with interferon and prone to similar side effects.

Patients treated with interferon can expect to experience such psychiatric side effects as development of depression, mania, irritability, changes in personality, hallucinations or delirium.

"In addition, certain patients are considered to be at greater risk of developing neuropsychiatric side-effects," they noted, especially if they are older than 40, have central nervous system abnormalities, a previous neurological or psychiatric history, a family history of psychiatric disorders, are HIV-infected, or have abused narcotics or alcohol.

Adefovir Lowers HBV DNA in Transplant Patients with Lamivudine Resistance

Researchers found the antiviral adefovir (Hepsera) was effective against HBV that had four types of mutations that allowed them to replicate even when lamivudine was used.

Writing in the January 2005 issue of the *Journal of Viral Hepatology*, researchers affiliated with Gilead Sciences examined the HBV of 131 liver transplant patients whose viruses had developed resistance to lamivudine and were experiencing a surge in HBV DNA and ALT levels.

They closely examined the HBV and found four types of mutations. The antiviral adefovir was effective in lowering HBV DNA levels in all four lamivudine-resistant mutation patterns.

