

# HBV JOURNAL REVIEW

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## Hepatitis B

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### Roche Asks FDA for Permission to Market Pegasys for Hepatitis B

In late July, Hoffmann-La Roche asked the U.S. Food and Drug Administration (FDA) for permission to market its pegylated interferon product, Pegasys, for the treatment of hepatitis B.

In clinical trials, pegylated interferon, which is a time-release interferon that requires only one weekly injection, has proved to be twice as effective as conventional interferon against hepatitis B.

In three clinical trials, Roche tested Pegasys in 1,500 chronic hepatitis B patients. A phase

II study compared Pegasys to standard interferon in patients with HBeAg-positive disease. Two phase III studies compared Pegasys to the antiviral lamivudine (Epivir-HBV) in patients with HBeAg-positive disease and in patients with HBeAg-negative disease (a more difficult to treat mutation of the hepatitis B virus).

The two studies are the largest trials conducted to date in patient populations infected with either variation of hepatitis B. Pegasys consistently outperformed both conventional interferon and lamivudine in lowering viral load, reducing liver damage, and spurring production of the “e” antibody.

Pegasys, commonly used to treat hepatitis C

in combination with the antiviral ribavirin, was administered at the same dosage (180 micrograms once a week) in the hepatitis B clinical trials as is currently used to treat hepatitis C.

Roche’s FDA application focuses only on Pegasys as a single treatment against hepatitis B – not used in combination with any antiviral.

When asked which hepatitis B patients would benefit from Pegasys, Roche spokeswoman Pamela Van Houten said, “We will need to see what the FDA permits us to say in our labeling. So far, Pegasys has been studied in HBeAg-negative and HBeAg-positive patients. Our

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studies showed that patients with low baseline ALT, high baseline HBV DNA, and HBV genotype C were less likely to respond to treatment.”

Roche has asked the FDA for an expedited review of its Pegasys application. If the FDA agrees to accelerate its review, approval of Pegasys for hepatitis B could come as early as January 2005. If the FDA does not give Pegasys priority review, a decision may not be rendered until mid-2005.

### HBV Genotypes and Precore Mutations Studied in Transplant Patients

Israeli researchers, reporting in the August issue of the journal *Clinical Transplant*, studied the role that viral load (HBV DNA level), hepatitis B genotype, and presence of the precore mutation in the virus played in the health of 50 hepati-

tis B patients who received liver transplants. Those studied (40 male, 10 female) represented a mix of people from nearly all racial and ethnic groups.

When they were transplanted, all patients had undetectable HBV DNA. Hepatitis B virus (HBV) genotype D was the most prevalent (96%) in the group, while genotype A was found in only 4%.

Eleven patients (22%) developed recurrent HBV infection after transplantation. There were no differences in genotype distribution between patients with and without recurring HBV infection, and those who developed viral resistance to the antiviral lamivudine.

The stable group, without HBV reinfection, had a similar origin and HBV genotype prevalence, but a lower viral load. The prevalence of precore mutations was similar in both groups.

Researchers concluded that patients with precore mutations typically had genotype D, but that genotype played no role in the rate or recurrence of HBV infection in patients with transplanted livers.

### Researchers Study Why Liver Cancer Hits Some Young Hepatitis B Patients

Japanese researchers, writing in the June issue of the *Journal of Gastroenterology*, studied four hepatitis B patients under the age of 30 who developed liver cancer without first developing cirrhosis.

Usually, most hepatitis B patients experience years of liver damage and cirrhosis before liver cancer appears.

When they were diagnosed, all four patients had developed “e” (HBeAg) antibodies. All of them had also been infected at birth by their HBV-infected mothers. The mothers of all four young adult patients also had HBV-related liver disease.

Based on this research, the doctors suggest that transplacental transmission of HBV and HBV DNA integration into liver cells DNA while the patients were still fetuses, “is a possible explanation of HBV-related hepatocarcinogenesis (liver cancer) in young adults.”

Three patients who developed recurring liver cancer after liver tumors were removed surgically, were treated with long-term, intermittent interferon therapy. The researchers found long-term interferon therapy, “seems to be useful for prevention of tumor recurrence after radical operation for HBV-related HCC (liver cancer).”

### Phase II Dosage Trials of Clevudine Successful

#### Phase II Dosage Trials of Clevudine Successful

A phase II, multi-center drug trial examined the impact of different doses of the antiviral clevudine on 32 hepatitis B patients over 28 days. The drug, a pyrimidine analog, was dosed at 10, 50, 100, and 200 mg once daily.

Most of the patients were male, of Asian descent, and had the “e” (HBeAg) antigen with elevated HBV DNA.

After 28 days, median HBV DNA levels

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dropped substantially. Six of 27 patients lost HBeAg, and 3 of 27 patients seroconverted to “e” antibody. Clevudine was well tolerated, with no dose-limiting issues appearing.

There was a short-lived increase in ALT (alanine aminotransferase) of up to 7.8 times the upper limit of normal (increases ranged from 20 to 186 IU/L) in six patients in the 100-mg cohort, without signs of liver failure. These increases were associated with improved suppression of HBV by the immune system.

The researchers, writing in *Hepatology* 2004, say these early clinical trial results show clevudine deserves additional clinical study.

**Why Do Some Lab Tests Miss HBV Infections?**

French researchers, writing in the August 2004 issue of the *Journal of Medical Virology*, investigated why some commercial lab tests miss “occult” or hidden HBV in blood tests. Most of these devices test for the sur-

face antigen component of the virus in a blood sample.

Finding hepatitis B is critical when blood or organs are tested before they are donated to patients.

Researchers looked for possible mutations in the surface antigen, the protein that covers the hepatitis B virus, which might mask the surface antigen and make it unrecognizable to lab tests.

Researchers found surface antigen mutations could indeed contribute to incorrect test results, but “in most cases the explanation is probably the low level of viral replication,” they concluded.

**Researchers Study Wide Range of HBV Genotype in San Francisco**

Researchers studied the genotype, liver health, and “e” antigen (HBeAg) status in 165 hepatitis B patients in the San Francisco area in an effort to better understand how genotype affects the progression of HBV infections.

Writing in the August 2004 issue of the *Journal of Medical Virology*, investigators reported that genotype A occurred in 60 (36%) patients, B in 16 (10%), C in 56 (34%), D in 19 (12%), E in 1 (1%), F in 1 (1%), G in 8 (5%), and H in 4 (2%). Caucasians were infected primarily with genotype A, Asians with genotype C, and Hispanics with genotypes F and H.

ALT levels were higher in patients infected with genotypes A or G compared to those with genotypes C.

HBeAg was more frequent in patients infected with genotypes G.

**Liver Cancer in HIV-HBV Coinfected Remains a Threat, Despite Therapy**

Two researchers, writing in the 2004 *Southern Medical Journal*, examined the threat that resolved and current hepatitis B infections pose to the HIV-HBV-infected. It is estimated that 64 to 84% of HIV-infected individuals have been in-

fectured with HBV, and 16% of those with HIV are coinfecting with active hepatitis B infections.

They reported on a coinfecting 44-year-old man who had liver cancer, despite low HBV DNA (viral load). While highly active antiretroviral therapy (HAART) has dramatically improved the outlook of those with HIV, coinfecting populations are still at risk. One report found that chronic viral liver disease represented 45% of in-hospital deaths among HIV-infected individuals.

Reappearance of HBV in newly HIV-infected patients and in patients who developed AIDS has been reported, even in patients who had cleared hepatitis B and developed hepatitis B surface antibodies.

The case illustrates that despite the advent of HAART, death from underlying chronic, non-HIV-related diseases, such as hepatitis B and liver cancer, “will likely continue to increase in the HIV-infected patient population,” researchers noted.

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**HBV DNA Test Results Can Be Imprecise**

Healthcare workers infected with HBV are often tested for HBV DNA (viral load) to determine how infectious their blood and body fluids are. These results can influence their career and scope of duties.

Writing in the August 2004 issue of the *Journal of Medical Virology*, German researchers examined how reliable the Amplicor HBV Monitor and the HBV Test Hybrid Capture II testing devices were, as well as an “in house” quantitative HBV TaqMan PCR tester. They analyzed and compared 101 blood samples from surface antigen-positive patients. In addition, HBV DNA concentrations were followed in 14 healthy chronic carriers for up to six years.

Despite a good overall correlation between the three tests, considerable differences were

found in individual blood tests. Fifty-one percent of blood showed differences within one order of magnitude, 45% differed by a factor above 10 and 4% by a factor of even 100 and higher.

The follow-up of the HBV DNA concentrations in 14 carriers showed a rather stable course with variations within one order of magnitude in seven carriers, whereas in the other half the DNA concentrations fluctuated by factors between 100-fold and 1,000,000-fold over the observation period.

The researchers concluded that HBV DNA levels in health care workers must be interpreted with some caution.

**Prevalence of Hepatitis B Infection after Kidney Transplants Studied**

Despite signs of immunity (presence of the surface antibody) due to immunization or a resolved hepatitis B

infection, some seemingly immune kidney transplant patients become infected with hepatitis B following their surgeries.

Writing in the August 2004 issue of the *Journal of Gastroenterology and Hepatology*, South Korean researchers explored the possibility that some mutated HBV are able to infect the liver despite the presence of the surface antibody, which should ward off hepatitis B infection.

Of 1,682 patients who were HBsAg negative before transplantation, 21 became HBsAg positive, with elevated ALT (alanine aminotransferase) levels after transplantation. Six had surface antibodies prior to transplantation. Analysis of HBV from two of six patients with immunity showed no evidence of significant viral mutations.

Seven of the 21 patients died from HBV-related complications.

The researchers concluded that regardless of hepatitis B immunity, infection occurs in immunosuppressed patients in areas with high

rates of HBV infection. They encouraged additional research into how this HBV infection occurs, given that many of these patients appeared to be immune to hepatitis B.

**Scientists Use Test to Track and Subdivide Genotype A**

The eight HBV genotypes have different geographical distributions, virological features, and clinical outcomes. Researchers investigated if patients infected with a variety of genotype A subtypes had different clinical outcomes than other genotype A subtypes. They studied genotype Aa (“a” for African and Asian subtype) and Ae (“e” for European subtype).

They compared 30 HBV/Aa and 30 HBV/Ae patients and found that almost all HBV/Ae viruses had a slightly different genetic make-up.

Taking advantage of

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this distinction, they tested the blood from 109 paid donors in the United States and found significant distributions of HBV/A subtypes. African-Americans, Caucasians, and Hispanics had HBV/Ae subtype, while Asians had mainly HBV/Aa, suggesting that the HBV/Aa isolates may have been imported by recent immigration from Asia.

**Natural Lymphoblastoid Interferon Shows Promise against Hepatitis B**

Researchers reported that natural lymphoblastoid interferon alpha may be a more promising drug against hepatitis B than conventional interferon, and it appears to be more effective in female hepatitis B patients than males.

Reporting in the July 2004 issue of the *Journal of Viral Hepatitis*, researchers wrote that they followed 210 pa-

tients in two trials. Some (34) received a placebo, and some received prednisolone priming before getting treatment with either conventional interferon or lymphoblastoid interferon.

They reported that the cumulative sustained response was higher in patients who were treated with lymphoblastoid interferon after prednisolone priming.

Liver cancer was detected in 1.5% of the lymphoblastoid interferon-treated group, 3.7% of the conventional interferon-treated group, and 14.7% of the control group who received placebo.

**Only 75% of HBV-Infected Children Achieve Immunity after Hepatitis A Vaccine**

Researchers, studying the immune response of children with chronic viral hepatitis to the hepatitis A vaccine, found that only 75 percent of children in-

fectured with HBV develop enough hepatitis A antibodies to fight off infection following immunization.

Hepatitis A vaccination is recommended for all children and adults with chronic hepatitis B or C. The vaccine against the widespread hepatitis A is designed to prevent a new and potentially deadly infection to an already infected liver.

Writing in the June 2004 issue of the *Pediatric Infectious Disease Journal*, researchers reported that after injections at one and six months with the HAVRIX 720 Junior hepatitis A vaccine, about 92% of children with hepatitis C developed a sufficient protective immune responses (anti-hepatitis A virus  $\geq 20$  mIU/ml), while only 75% of children with chronic hepatitis B developed adequate antibody protection.

About 91% of healthy children developed adequate immune protection following hepatitis A immunization.

Researchers noted that a hepatitis A booster produced adequate immune protection in all children.

**Plant-Made Antibody Targets Hepatitis B Virus**

Japanese scientists have successfully used genetically-engineered tobacco plant cells to produce an antibody that targets and destroys the surface antigen (HBsAg) of the hepatitis B virus.

Currently, surface antibodies, called immunoglobulin, is collected from blood donors and is very expensive.

“Or plant-derived (antibody) has the potential to be a cheap and effective pharmaceutical,” for the prevention and treatment of HBV infection, said Dr. Akira Yano from the National Institute of Public Health in Tokyo, who wrote about the plant-made antibody in the 2004 *Journal of Medical Virology*.

Yano recommends the use of plant-derived antibodies over blood-derived antibodies to reduce the risk of blood-borne infections.

Yano reported that eventually biopharmaceuticals derived from geneti-

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cally-modified plants could become “safe and economical for promotion of global health.”

### Federal Survey Finds Young Children Lack Vaccines

More than 20 percent of preschool children lack required immunizations, including the hepatitis B vaccine, according to CDC researchers writing in the American Journal of Preventive Medicine.

While public schools require immunization prior to enrollment, most childcare facilities lack that entry requirement. Researchers report that only 76% of toddlers ages 19 to 35 months were immunized. Of the preschoolers who were not up to date on vaccinations, more than 90 percent were missing more than one dose.

Vaccines in the survey included diphtheria, tetanus, pertussis, polio, measles, hepatitis B and Haemophilus

influenzae type b (Hib).

“Revised strategies and more effort are needed to improve coverage of children who attend and do not attend childcare programs,” researchers proposed.

### Prisoners Willing to Get Hepatitis B Vaccine

Ninety-three percent of Rhode Island inmates studied said they would agree to receive the hepatitis B vaccine in prison if it were offered, according to a Brown University research report. Although vaccination has been available for two decades, 1.2 million Americans have chronic hepatitis B, and the disease continues to spread among prison populations.

Currently, about 20% of incoming inmates test positive for hepatitis B, which is easily transmitted through blood and body fluids.

The authors of the study recommend vac-

inating all prisoners against hepatitis B, noting that 3 percent of the inmates contracted the virus within the first 12 months of incarceration.

Only two prison facilities in the United States currently vaccinate incoming prisoners against hepatitis B.

“Implementation of routine hepatitis B vaccination in jails and prisons could substantially decrease hepatitis B transmission by preventing disease in ... those most at risk,” reported Snigdha Vallabhaneni, study author and third-year student in the Brown Medical School. “Such programs would help protect the health of incarcerated persons and the communities to which they return.”

### New Vaccine Agents under Investigation

At the 12th International Congress of Immunology and 4th Annual Conference of the Federation of Clinical

Immunology Societies, jointly held in Montreal, Dr. Cristina Ciurli of Bioniche Therapeutics presented reports on two new immune agents that could strengthen the hepatitis B vaccine.

The two Oligomodulators were found to increase the level of antibodies the immune system produces when a person is vaccinated with the hepatitis B surface antigen.

“Our results show that these two Oligomodulators may have potential for immunization against a wide variety of antigens, not only for the hepatitis B surface antigen,” added Dr. Ciurli. “The unexpected adjuvant activity of our Oligomodulators following oral administration offers significant advantage over the established intramuscular (injection) route of vaccination.”

Oligomodulator oligodeoxynucleotides are a class of molecules with potential anti-cancer activity and immune-modulating properties.

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### **Roche Recalls Hepatitis B Test Analyzers**

Roche Molecular Systems Inc. has recalled its COBAS TaqMan Analyzers and COBAS TaqMan 48 Analyzers, used by laboratories to test for hepatitis B and C viruses, after several experienced mechanical problems that delivered falsely elevated test results.

Falsely elevated results would suggest that a patient was not responding to treatment, or had a different stage of infection.

In extreme cases, the company reported, the misalignment of the fiber optic cable in the device could result in a mismatch of patient test results.

Roche began its investigation after one customer complained. It stated that to date, no patient was inappropriately treated as a result of this mechanical problem.

Roche Diagnostics have notified its customers of the problem and has inspected all

instruments to assure proper alignment of the device's fiber optic cable.

### **Korean Red Cross Missed 2,000 Hepatitis B and C Cases among Donors**

The Korean Red Cross announced that about 2,000 blood donors, some of whom were infected with hepatitis B or C, were "misdiagnosed" and allowed to donate blood to hospitals during the last 10 years.

This is the first time it has been revealed that the blood of hepatitis-infected individuals was used for transfusions or to make medical supplies due to Red Cross staff carelessness or mistakes.

According to South Korea's Health and Human Welfare Ministry, a review of blood donation conditions since 1994 yielded seven blood donation centers nationwide where tainted blood was received.

The 2,000 misdiagnosed cases included cases in which donors who were infected

tested negative and were allowed to donate, and those whose blood was used even though it tested positive for bloodborne viruses.

The Welfare Ministry said at a certain blood bank in 2002, there were 13 cases in which hepatitis-positive blood was diagnosed as negative, and 16 in which hepatitis-negative blood was initially diagnosed as positive. If the ministry confirms that some of the blood was supplied to hospitals for use, it will track down who received the blood and provide compensation to those who were infected.

The hepatitis B virus is a resilient virus that can live in blood for several days outside the body.

### **Researchers Test Disinfectants against Hepatitis B**

Researchers, reporting in the Journal of Hospital Infection, tested several new chemical disinfectants for their effectiveness against HBV-tainted blood

over three days at different solutions.

Today, many health-care workers use alcohol disinfectant hand rubs instead of soap and water to prevent the spread of infections.

A total of 37 tests were performed on 12 products, with up to three concentrations and three exposure times. Researchers said two of the three surface disinfectants and two of the three instrument disinfectants were highly active at whatever concentrations and time exposures used.

However, other products such as one of the surface disinfectants was only active at concentrations above 0.5% for 15 minutes.

Similarly, the skin disinfectant, one of the instrument disinfectants, and the hand wash agent (diluted to 50%) were less or not active. This is the first study using a cell culture model to assess disinfectant activity of new disinfectants against HBV.