

HBV JOURNAL REVIEW

Volume 2, Issue 8

August 01, 2005

Hepatitis B

Christine Kukka

Pegylated Interferon Should Be First Treatment for HBeAg-Positive Patients

Doctors who make up the Peginterferon Alfa-2a HBeAg-Positive Chronic Hepatitis B Study Group say pegylated interferon may be a better first-time treatment than the antiviral lamivudine (Epivir-HBV) in people who have the hepatitis B “e” antigen (HBeAg).

The findings, reported by Dr. George K.K. Lau of the University of Hong Kong in the June 30 issue of the *New England Journal of Medicine*, were based on a study of 814 patients.

The patients received

either pegylated interferon plus a placebo, or pegylated interferon plus the antiviral lamivudine for 48 weeks. Interferon boosts the immune system to fight infection, while an antiviral tampers with the hepatitis B virus’ (HBV) genetic material so it cannot reproduce effectively.

The patients who had HBV genotypes B or C were followed for 24 weeks after treatment.

After 24 weeks, 32% of interferon-only patients and 27% who received both interferon and lamivudine seroconverted and developed the “e” antibody. No patients who received only lamivudine seroconverted.

Hepatitis B surface antigen (HBsAg) seroconversion (production of the surface antibody, which generally indi-

cates a complete cure) occurred in 16 patients who received interferon alone or in combination with lamivudine.

Serious side effects, including depression that is common with interferon, occurred in 4% of patients receiving just interferon and in 6% who received the combination treatment.

“In patients with HBeAg-positive chronic hepatitis B, (pegylated interferon) offers superior efficacy over lamivudine, on the basis of HBeAg seroconversion, HBV DNA suppression, and HBsAg seroconversion,” the authors wrote. “The ability to achieve HBeAg and HBsAg seroconversion after a defined period of (pegylated interferon) therapy supports the use of (interferon) as a first-line therapy for patients with HBeAg-positive chronic hepatitis B.”

HBV Journal Review
A publication of the Hepatitis C
Support Project

Executive Director
Editor-in-Chief,
HCSP Publications
Alan Franciscus

Contributor
Christine Kukka

Managing Editor,
Webmaster
C.D. Mazoff, PhD

Contact Information:
The Hepatitis C Support
Project
PO Box 427037
San Francisco, CA 94142

www.hbvadvocate.org

© 2005
Hepatitis C Support Project

Human Protein Could Play Role in Reducing Hepatitis B Viral Replication

Scientists have discovered a human cellular protein, called hnRNPK, that apparently plays a significant role in preventing viral replication and liver cancer.

Researchers, reporting in the July issue of the *Public Library of Science Medicine* journal, say this cellular protein can keep HBV replication in check and prevent high viral load (HBV DNA).

Researchers identified the protein when they found that HBV with a particular mutation caused extremely high viral load. They discovered that the rate of viral reproduction was determined by its mutated, genetic make-up as well as how well hnRNPK was able to bind to the viral DNA and slow its replication.

Researchers suggest this human protein could someday become a new treatment option in addition to antivirals

and interferons, to slow or stop HBV replication.

Lowering viral load is essential because high levels of HBV DNA can result in serious liver damage and development of liver cancer.

Scientists Discover How HBV Short-Circuits Cancer-Suppressing Enzymes

Researchers at the MD Anderson Cancer Center in Houston have determined how HBV shuts down a tumor-suppressing enzyme known as GSK-3b, which then allows liver cancer to develop. In healthy cells, GSK-3b prevents beta catenin, which allows development of cancer, from entering cells. But when GSK-3b is "turned off," beta catenin accumulates to harmful levels inside the cell's nucleus and leads to cancer, researchers reported in the July 21 issue of the

journal *Molecular Cell*. A similar mechanism may be involved in the development of other cancers, including breast, colon, kidney, and stomach cancers. Researchers examined 53 liver tumors to study how the GSK-3b mechanism worked. They discovered two other key molecular players in this sequence: the HBV viral protein known as HBX and another cellular enzyme identified as Erk. HBX activates Erk, which in turn binds to and inactivates GSK-3b. This is how HBV reportedly shuts down GSK-3b.

In a second series of experiments, the researchers found a way to stop the process. They introduced a variant form of GSK-3b into liver cancer cells. This form could not be inactivated by Erk because the binding site for Erk had changed. The new form of GSK-3b once again began clearing away the harmful protein beta catenin. In theory, this would inhibit the proliferation of new cancer cells, the researchers said.

Researchers suggest that development of gene therapy and mole-

cules that activate GSK-3b may one day provide effective treatment for liver and other cancers.

Emtricitabine Lowers HBV DNA, But 18% Develop Viral Resistance in Two Years

A two-year study that examined the best dosage levels of the antiviral emtricitabine (FTC), found 200 mg was the best and safest dosage. After two years, 53% of the patients had undetectable HBV DNA, 33% seroconverted (produced the "e" antibody) and 85% achieved normal alanine aminotransferase (ALT) levels. (When ALT levels are elevated, it means liver cells are damaged.) However, 18% of patients who received the 200-mg emtricitabine dose for two years developed viral resistance to the drug.

The study, led by Dr. Robert Gish, was reported in the July 2005 issue of the *Journal of Hepatology*.

Dried Blood Samples on Paper Filters Accurately Show Hepatitis B Status

Testing people for hepatitis B and related liver cancer, especially in poor or developing countries, is a challenge because of the cost required to collect, transport and store blood samples.

A team of researchers, reporting in the July 2005 issue of the *Journal of Viral Hepatitis*, has found a way to collect blood samples on filter paper, and then accurately test the samples for HBsAg and alpha-fetoprotein (AFP), a substance that indicates the presence of cancerous tumors.

Three to five blood drops were dried on filter paper and tested for HBsAg by Determine™ HBsAg and for AFP by counter-current immuno-electrophoresis and radio-immunoassay (RIA).

The test identified HBsAg 96% of the time, and it detected AFP 73% of the time. The accuracy of the tests was not affected

when the samples were left at room temperature and under humid conditions for up to 28 days before testing.

“We conclude that (dried blood samples) can be reliably used as an economical and logical alternative for detection of HBsAg in chronically infected patients and for AFP-based diagnosis of HCC (liver cancer) in clinical situations which preclude adequate collection and processing of blood samples,” researchers reported.

Adefovir Effective Against HBeAg-Negative Hepatitis B into Third Year

Gilead Sciences, developer of the antiviral adefovir (Hepsera), has published a report in the *New England Journal of Medicine*, that shows adefovir is effective against a mutated strain of HBV that is able to replicate without secreting HBeAg, known as

HBeAg-negative hepatitis B.

The drug company followed 80 patients with HBeAg-negative hepatitis B who received adefovir for 144 weeks.

The antiviral, which meddles with the viral genetic material to prevent viral reproduction, continued to be effective in keeping viral load down and preventing liver damage.

Among the patients, 71% achieved undetectable viral load at week 96, and 79% had undetectable HBV DNA levels at week 144.

In this study, however, six of 80 patients (7.5%) who received adefovir developed viral resistance to adefovir during the second year of the study. When viral resistance develops, the antiviral loses its ability to suppress HBV replication. When that occurs, a patient’s viral load (HBV DNA) and ALT levels gradually begin to increase again.

Researchers also stressed the importance of continuing adefovir for more than 48 weeks, noting that its beneficial effects were lost if treatment ended too soon.

Antiviral Lamivudine Has Little Success Against Hepatitis D

A team of researchers, writing in the *Alimentary Pharmacology & Therapeutics* medical journal, reported that lamivudine (Epivir-HBV) had little success against hepatitis D.

Hepatitis D viruses require surface antigen (HBsAg) from the hepatitis B virus in order to reproduce. Consequently, a hepatitis B infection must be present in order for hepatitis D virus to infect the liver. Hepatitis D is most common in the Mediterranean region.

Researchers treated 31 patients who tested positive for both HBsAg and hepatitis D RNA and had elevated ALT levels with either placebo or 100 mg of lamivudine daily for one year, and then followed patients for 16 weeks.

None of the patients cleared HDV-RNA by week 52; but three patients (11%) were negative at week 104

and two remained HDV-RNA-negative at week 120. One patient lost HBsAg without seroconversion.

Researchers reported that a sustained response was achieved in only 8% of hepatitis D virus-infected patients treated with lamivudine, though liver health improved in 26%.

However, hepatitis D virus was unaffected, even in patients who had reduced HBV viral load.

Simple Oral Test Could Replace Blood Draw for Hepatitis B Screening

Belgium researchers, reporting in the July issue of the *Journal of Medical Virology*, say they have developed an oral test for hepatitis B, which would make it easier to test large numbers of people.

Currently, a blood sample is required to test people for HBsAg, which indicates an active infection.

Doctors tested their

oral ETI-MAK-4 ELISA test on the saliva of 43 HBsAg-positive and 73 HBsAg-negative patients, and the oral test results were accurate 90.7% and 100% of the time, respectively.

Lamivudine-Resistance Poses Risks in Transplant Patients with Genotype C

Researchers studied the differences between transplant patients with either HBV genotype B or C and found that genotype C carried a higher risk of severe hepatitis B recurrence due to the presence of HBV that could resist lamivudine's antiviral effects because of their mutations.

Writing in the August 2005 issue of the *American Journal of Transplantation*, researchers described following 117 genotype B and C patients for three years after liver transplantation.

Genotype B patients had significantly more

pre-transplant flares and liver damage. Fewer genotype B patients had HBeAg compared to those with genotype C (13% vs. 32%), but viral load was similar in both groups.

The three-year survival rate was 83% for genotype B and 89% for genotype C, and the rate of HBsAg clearance or seroconversion was similar in both groups.

But the rate of viral breakthrough due to lamivudine-resistant HBV, as indicated by an increase in HBV DNA and elevated ALT levels, was 4% for genotype B and 21% for genotype C at the three-year mark.

Liver biopsies showed recurrent HBV infection in seven of 10 genotype C patients, but there was none in genotype B patients.

"In conclusion," researchers wrote, "HBV genotypes B and C are associated with different patterns of end-stage liver diseases that required transplantation, and genotype C may carry a greater risk and severity of recurrence due to lamivudine-resistant mutants."

Undetected HBV May Cause Liver Cancer after Hepatitis C Is Cured

Coinfection with hepatitis B and C viruses is common, but hepatitis C often emerges as the "dominant" virus when lab tests are performed and can mask the presence of a past or present HBV infection.

Writing in July 2005 issue of *The American Journal of Gastroenterology*, doctors reported studying seven liver cancer survivors who years earlier had been cured of hepatitis C following interferon treatment. They found HBV DNA in four of the patients liver tumors. HBV DNA was not present in the patients' blood, but it had integrated into the cancers.

"Integrated HBV DNA may play a role in hepatocarcinogenesis (development of liver cancer) after the clearance of hepatitis C by interferon treatment," researchers concluded.

Doctors Learning More About Why Therapeutic Vaccines Don't Work

For several years, researchers have tried unsuccessfully to develop a therapeutic vaccine for HBV-infected patients. They hoped the vaccine, which contains a non-infectious portion of the virus, would “wake up” the immune system and cause it to attack the HBV infection.

Recently, scientists at The Wistar Institute and Emory University have discovered what may prevent the immune system from responding to therapeutic vaccines when a chronic infection is present. Writing in the July 2005 issue of the *Journal of Virology*, the scientists also report they may have discovered how to make these therapeutic vaccines work.

They found that T cells in chronically-infected mice responded poorly to therapeutic vaccines,

probably due to the overwhelmingly high viral load. Researchers hypothesize that lowering viral load before administering the vaccine may make it more effective.

The next step will be to combine vaccines with antivirals or drugs that enhance T cell function, such as cytokines that promote reproduction and survival of T cells.

CDC Committee Urges Immediate HBV Immunization of Newborns

In late June, the U.S. Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices proposed stricter hepatitis B vaccine recommendations. Current guidelines recommend the first of three HBV vaccine dose be given within two hours of birth, but they allow the first dose to be given up to two months of age if the mother is HBV-negative.

If approved by CDC

administrators, the new recommendations would have doctors administer the first vaccine dose before infants leave the hospital, even if mothers test negative for HBV.

Childhood Vaccination Campaign Against Hepatitis A Appears Effective

A report published in the July 13 *Journal of the American Medical Association* shows that targeted vaccination of children in 17 high-risk states has greatly reduced hepatitis A infections nationwide since 1999. Infections fell 76 percent to 7,653 cases in 2003, the lowest recorded rate of infection since the 1960s.

The vaccination program has reduced infection rates even more dramatically among children aged two to nine years, from 18.1 cases per 100,000 children to two cases per 100,000 in the last six years, an 89 percent decline.

The vaccination strategy of targeting children in 17 high-risk states, mostly in the West and Southwest, grew out of an analysis of hepatitis A infection rates in the late 1990s which showed that a majority of U.S. cases were concentrated in those states.

The hepatitis A vaccination is recommended for anyone with hepatitis B or C.

